=> fil reg
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DICTIONARY FILE UPDATES: 19 JUN 2002 HIGHEST RN 432491-02-6

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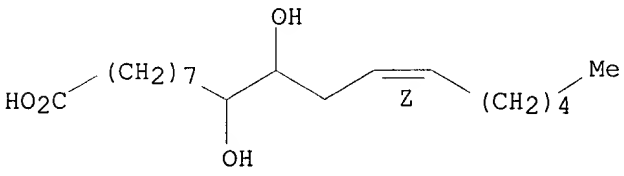
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can tot l70

L70 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN **263399-34-4** REGISTRY
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (12Z)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C18 H34 O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:163965

REFERENCE 2: 134:143071

REFERENCE 3: 133:360357

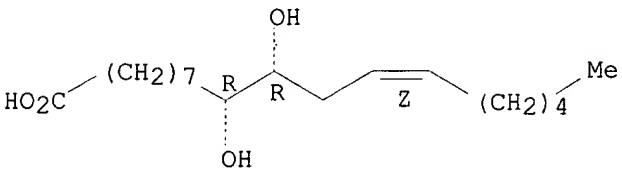
REFERENCE 4: 132:262485

L70 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN **189191-41-1** REGISTRY
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 12-Octadecenoic acid, 9,10-dihydroxy-, [R*,R*-(Z)]-
OTHER NAMES:
CN Leukotoxin diol

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

FS STEREOSEARCH
DR 59959-42-1
MF C18 H34 O4
SR CA
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

9 REFERENCES IN FILE CA (1967 TO DATE)
9 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:116492

REFERENCE 2: 133:70547

REFERENCE 3: 132:318802

REFERENCE 4: 132:318745

REFERENCE 5: 131:168305

REFERENCE 6: 129:36394

REFERENCE 7: 128:201056

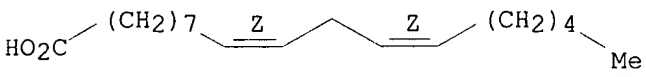
REFERENCE 8: 127:230447

REFERENCE 9: 126:289133

L70 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN **60-33-3** REGISTRY
CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 9,12-Octadecadienoic acid (Z,Z)-
CN Linoleic acid (8CI)
OTHER NAMES:
CN (Z,Z)-9,12-Octadecadienoic acid
CN .alpha.-Linoleic acid
CN 9,12-Octadecadienoic acid, (Z,Z)-
CN 9-cis,12-cis-Linoleic acid
CN 9Z,12Z-Linoleic acid
CN all-cis-9,12-Octadecadienoic acid
CN cis,cis-Linoleic acid
CN cis-.DELTA.9,12-Octadecadienoic acid
CN cis-9,cis-12-Octadecadienoic acid
CN Emersol 315
CN Extra Linoleic 90
CN Linolic acid
CN Polylin 515
CN Unifac 6550

FS STEREOSEARCH
MF C18 H32 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, ENCOMPLIT, ENCOMPLIT2, ENCOMPPAT, ENCOMPPAT2, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, TULSA, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

24941 REFERENCES IN FILE CA (1967 TO DATE)
1106 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
24987 REFERENCES IN FILE CAPLUS (1967 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 136:395039

REFERENCE 2: 136:393328

REFERENCE 3: 136:391350

REFERENCE 4: 136:391071

REFERENCE 5: 136:391045

REFERENCE 6: 136:390753

REFERENCE 7: 136:390501

REFERENCE 8: 136:387668

REFERENCE 9: 136:387667

REFERENCE 10: 136:387465

=> d his

(FILE 'REGISTRY' ENTERED AT 16:28:38 ON 21 JUN 2002)
DEL HIS
E LINOLEIC ACID/CN
L1 1 S E3
L2 5 S C18H32O2/MF AND 9 12 OCTADECADIENOIC ACID NOT (LABELED OR (D

FILE 'HCAPLUS' ENTERED AT 16:30:25 ON 21 JUN 2002
E LEUKOTOXINDIOL
L3 15 S E1,E4,E5 (L) DIOL

FILE 'REGISTRY' ENTERED AT 16:32:01 ON 21 JUN 2002

```
L4            1 S 189191-41-1
L5           10 S C18H34O4/MF AND 12 OCTADECENOIC ACID  AND 9 10 DIHYDROXY NOT
L6           10 S L4,L5

     FILE 'HCAPLUS' ENTERED AT 16:33:44 ON 21 JUN 2002
L7           33 S L6
L8           39 S L3,L7
L9          100 S (L1 OR LINOLEIC ACID)(L)DIOL
L10         125 S L8,L9
L11           8 S L10 AND (?HYPERTENS? OR ARDS OR (ADULT OR ACUTE)(L)RESPIR?(L)
                E HAMMOCK B/AU
L12         510 S E3-E8
                E ZUREK G/AU
L13           8 S E3,E4
                E GEE S/AU
L14         148 S E3-E10,E21,E22
                E NEWMAN J/AU
L15          81 S E3,E29
                E NEWMAN JOHN/AU
L16         318 S E3,E36,E37
L17          12 S L10 AND L12-L16
                E CARDIOVASCULAR/CT
                E E6+ALL
L18          67 S E1
                E E2+ALL
L19        5360 S E4
L20      281115 S E3+NT
                E HYPERTENSION/CT
                E E3+ALL
L21       33653 S E2+NT
                E E8+ALL
L22       23168 S E3+NT
L23       40210 S E8+NT
L24      118127 S E7+NT
                E ADULT RESPIRATORY DISTRESS SYNDROME/CT
                E E3+ALL
L25          31 S E1
L26        1395 S E2
                E PREECLAMPSIA/CT
                E E3+ALL
L27        2169 S E3,E4,E2+NT
L28        3737 S E3-E9/BI
                E LIPID METABOLISM/CT
                E E3_ALL
                E LIPID METABOLISM/CT
                E E3+ALL
L29       11021 S E1,E2
L30           6 S L10 AND L18-L29
L31          14 S L11,L17,L30
                E FATTY ACIDS/CT
                E FATTY ACIDS(L)D/CT
                E UNSATURATED FATTY ACIDS/CT
                E E3+ALL
L32        8133 S E1,E2
L33          48 S L32 (L) (DIHYDROXY# OR DIOH OR DIOL OR DI HYDROXY# OR DI OH)
L34          13 S L33 NOT (PLASTIC# OR COATING?)/SC,SX
L35           3 S L34 AND (1 OR 9 OR 63)/SC,SX
L36         320 S L32 AND L18-L29
L37           5 S L36 AND 9/SC
                SEL DN 2
L38           1 S L37 AND E1
L39         422 S L32 (L) (ANT OR ANST)/RL
L40           6 S L39 AND L36
```

```
                SEL DN 3
L41           1 S L40 AND E2
L42          15 S L31,L38,L41
L43           1 S L10 (L) (ANT OR ANST)/RL
L44           0 S L10 AND (BLOOD ANALYSIS OR URINALYSIS)
L45           8 S L10 AND ?ASSAY?
                SEL DN 1 2 5
L46           3 S L45 AND E3-E5
L47          16 S L42,L46
L48           0 S L10 AND ELISA
L49           7 S L10 AND (BLOOD OR URINE)
                E BLOOD/CT
                E E3+ALL
L50           4 S L10 AND E2+NT
L51           0 S L10 AND (E136+NT OR E139+NT OR E145+NT)
                E URINE/CT
                E E3+ALL
L52           0 S L10 AND E3+NT
L53           1 S L10 AND E2+NT
L54           5 S L10 AND E1+NT
                E URINE ANALYSIS/CT
                E E3+ALL
L55           0 S L10 AND E3,E2+NT
L56          24 S L47,L49,L50,L53,L54
L57           9 S L56 AND L1,L2
L58          16 S L56 AND ?LINOLE?
L59          17 S L57,L58
L60           7 S L56 NOT L59
L61           6 S L60 NOT WASP
L62          23 S L59,L61
                SEL DN 6 18 19 20 21 22 23
L63          16 S L62 NOT E1-E7
L64          16 S L63 AND L3,L7-L63
L65          14 S L64 AND LEUKOTOX?
L66          16 S L64,L65
L67           7 S LINOLE? (L) ?GLUCURON? (L) ?CONJUGAT?
                SEL DN 1
L68           1 S L67 AND E8
L69          16 S L66,L68
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 17:05:40 ON 21 JUN 2002
L70           3 S E9-E11

     FILE 'REGISTRY' ENTERED AT 17:05:59 ON 21 JUN 2002

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 17:06:08 ON 21 JUN 2002
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FILE COVERS 1907 - 21 Jun 2002 VOL 136 ISS 25
FILE LAST UPDATED: 19 Jun 2002 (20020619/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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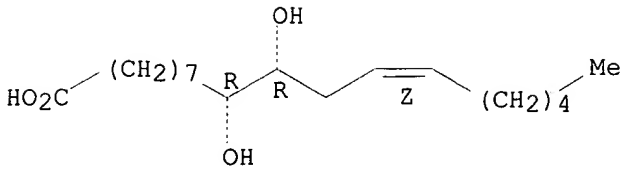
=> d all hitstr tot l69

L69 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:863088 HCAPLUS
DN 136:116492
TI **Leukotoxin-Diol**. A putative toxic mediator involved in **acute respiratory distress syndrome**
AU Zheng, Jiang; Plopper, Charles G.; Lakritz, Jeffery; Storms, David H.; **Hammock, Bruce D.**
CS Department of Pharmaceutical Sciences, School of Pharmacy, Bouve College of Health Sciences, Northeastern University, Boston, MA, 02115, USA
SO American Journal of Respiratory Cell and Molecular Biology (2001), 25(4), 434-438 Oct '01
CODEN: AJRBEL; ISSN: 1044-1549
PB American Thoracic Society
DT Journal
LA English
CC 14-4 (Mammalian Pathological Biochemistry)
AB **Leukotoxin** is clin. assocd. with **acute respiratory distress syndrome** (**ARDS**). Recently, we found that **leukotoxin-diol**, the hydrated product of **leukotoxin**, is more toxic than the parent **leukotoxin** in vitro. To test if this difference in the toxicity of **leukotoxin** and **leukotoxin-diol** exists in vivo, Swiss Webster mice were administered **leukotoxin** or **leukotoxin-diol**. All mice treated with **leukotoxin-diol** died of **ARDS**-like **respiratory distress**, whereas the animals exposed to **leukotoxin** at the same dose survived. Histopathol. evaluation of the lungs revealed massive alveolar edema and hemorrhage with interstitial edema around **blood** vessels in the lungs of mice treated with **leukotoxin-diol**, whereas the lungs of mice treated with identical doses of **leukotoxin** had perivascular edema only and little change in alveolar spaces. Immunohistochem. showed that the sol. epoxide hydrolase responsible for the hydrolysis of **leukotoxin** to its **diol** is concd. in the vascular smooth muscle of small and medium-sized pulmonary vessels. In addn., 4-phenylchalcone oxide, an inhibitor of sol. epoxide hydrolase, was found to decrease the mortality induced by **leukotoxin** but had no effect on mortality induced by **leukotoxin-diol**. These studies provide strong in vivo evidence that **leukotoxin** may act as a protoxicant and that the corresponding **diol** is a putative toxic mediator involved in the development of **ARDS**.
ST **leukotoxin diol** toxic mediator respiration distress syndrome
IT **Respiratory distress syndrome**
(**acute**; **leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
IT Lung
(alveolus; **leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory**

distress syndrome in mice)
IT Hydrolysis
(biol.; **leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
IT Lung, disease
(injury; **leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
IT Edema
Hemorrhage
(**leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**leukotoxins; leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
IT **Blood vessel**
(smooth muscle; **leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
IT **189191-41-1, Leukotoxin-Diol**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
IT 2403-28-3D, 4-Phenylchalcone, oxide 9048-63-9, Epoxide hydrolase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Demling, R; Annu Rev Med 1995, V46, P193 HCAPLUS
(2) Grant, D; Biochem Pharmacol 1996, V51, P503 HCAPLUS
(3) Hayakawa, M; Biochem Biophys Res Commun 1989, V161, P1077 HCAPLUS
(4) Hsu, S; J Histochem Cytochem 1981, V10, P1079
(5) Hu, J; Lung 1988, V166, P327 HCAPLUS
(6) Kosaka, K; Mol Cell Biochem 1994, V139, P141 HCAPLUS
(7) Lee, M; Science 1998, V280, P915 MEDLINE
(8) Moghaddam, M; Nature Med 1997, V3, P562 HCAPLUS
(9) Moran, J; Toxicol Appl Pharmacol 1997, V146, P53 HCAPLUS
(10) Mullin, C; Arch Biochem Biophys 1982, V216, P423 HCAPLUS
(11) Ozawa, T; Am Rev Respir Dis 1988, V137, P535 HCAPLUS
(12) Ozawa, T; Biochem Biophys Res Commun 1988, V152, P1310 HCAPLUS
(13) Plopper, C; Exp Lung Res 1987, V13, P59 HCAPLUS
(14) Street, J; J Biol Chem 1996, V271, P3507 HCAPLUS
(15) Vaitukaitis, J; Methods Enzymol 1981, V73, P46 MEDLINE
(16) Wixtrom, R; Anal Biochem 1988, V169, P71 HCAPLUS
IT **189191-41-1, Leukotoxin-Diol**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**leukotoxin-diol**. a putative toxic mediator involved in **acute respiratory distress syndrome** in mice)
RN 189191-41-1 HCAPLUS
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L69 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:539978 HCAPLUS
DN **135:148461**
TI Cellular Characterization of **Leukotoxin Diol**-Induced Mitochondrial Dysfunction
AU Sisemore, Marlene F.; Zheng, Jiang; Yang, Joy C.; Thompson, David A.; Plopper, Charles G.; Cortopassi, Gino A.; **Hammock, Bruce D.**
CS Department of Entomology, University of California, Davis, CA, 95616, USA
SO Archives of Biochemistry and Biophysics (2001), 392(1), 32-37
CODEN: ABBIA4; ISSN: 0003-9861
PB Academic Press
DT Journal
LA English
CC 4-5 (Toxicology)
Section cross-reference(s): 1, 14
AB **Leukotoxin**, a cytochrome P 450-derived epoxide of **linoleic acid**, has been implicated as a causative factor in **acute respiratory distress syndrome**. Conversion of this fatty acid epoxide to **leukotoxin diol** by epoxide hydrolase has been hypothesized as the crit. activation step in **leukotoxin**-induced cellular toxicity. In both human and insect cells, we obsd. that **leukotoxin diol** causes **acute** cellular toxicity and that cyclosporin A, an inhibitor of the mitochondrial permeability transition, ameliorates **leukotoxin diol**-assocd. toxicity. To evaluate mitochondria as a target of **leukotoxin diol**, multiple aspects of mitochondrial integrity were evaluated in both cell- and organelle-based **assays**. **Leukotoxin diol** specifically activated the mitochondrial permeability transition, resulting in release of cytochrome c and subsequent cell death. Pretreatment with cyclosporin A inhibited these effects and, furthermore, limited in vivo toxicity. While the mechanisms underlying **leukotoxin**-mediated toxicity remain to be fully elucidated, the observation that **leukotoxin diol** disrupts mitochondrial function specifically through activation of the mitochondrial permeability transition suggests at least one mechanism through which **leukotoxin diol** may exert its activity in physiol. contexts. (c) 2001 Academic Press.
ST **leukotoxin diol** mitochondria cell death
IT Animal cell line
(SF21, insect; cellular characterization of **leukotoxin diol**-induced mitochondrial dysfunction)
IT Cell death
HeLa cell
Mitochondria
Respiratory distress syndrome
(cellular characterization of **leukotoxin diol** -induced mitochondrial dysfunction)
IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**leukotoxins**; cellular characterization of **leukotoxin diol**-induced mitochondrial dysfunction)
IT 21019-43-2, Methyl **leukotoxin** 189191-42-2, Methyl **leukotoxin diol**

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cellular characterization of **leukotoxin diol**
-induced mitochondrial dysfunction)
IT 59865-13-3, Cyclosporin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cellular characterization of **leukotoxin diol**
-induced mitochondrial dysfunction)
IT 9007-43-6, cytochrome c, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cellular characterization of **leukotoxin diol**
-induced mitochondrial dysfunction)
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bossy-Wetzel, E; Embo J 1998, V17, P37 HCAPLUS
(2) Demling, R; Annu Rev Med 1995, V46, P193 HCAPLUS
(3) Green, D; Science 1998, V281, P1309 HCAPLUS
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(8) Ishizaki, T; Am J Physiol 1995, V268, PL123 HCAPLUS
(9) Kluck, R; Science 1997, V275, P1132 HCAPLUS
(10) Kosaka, K; Mol Cell Biochem 1994, V139, P141 HCAPLUS
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(14) Nieminen, A; Biochem J 1995, V307, P99 HCAPLUS
(15) Ozawa, T; Adv Prostaglandin Thromboxane Leukot Res 1991, P569 MEDLINE
(16) Ozawa, T; Am Rev Respir Dis 1988, V137, P535 HCAPLUS
(17) Sakai, T; Am J Physiol 1995, V269, PL326 HCAPLUS
(18) Tafani, M; Am J Pathol 2000, V156, P2111 HCAPLUS
(19) VanRollins, M; J Biol Chem 1996, V271, P14001 HCAPLUS
(20) Weintraub, N; Circ Res 1997, V81, P258 HCAPLUS
(21) Yang, J; Biochem Biophys Res Commun 1998, V250, P454 HCAPLUS
(22) Yang, J; Free Rad Biol Med 1998, V24, P624 HCAPLUS
(23) Yang, J; Science 1997, V275, P1129 HCAPLUS

L69 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:170554 HCAPLUS
DN 135:15220
TI The Role of Methyl-**Linoleic Acid** Epoxide and **Diol** Metabolites in the Amplified Toxicity of **Linoleic Acid** and Polychlorinated Biphenyls to Vascular Endothelial Cells
AU Slim, Rabih; **Hammock, Bruce D.**; Toborek, Michal; Robertson, Larry W.; **Newman, John W.**; Morisseau, Christophe H. P.; Watkins, Bruce A.; Saraswathi, Viswanathan; Hennig, Bernhard
CS Graduate Center for Toxicology, University of Kentucky, Lexington, KY, 40506-0054, USA
SO Toxicology and Applied Pharmacology (2001), 171(3), 184-193
CODEN: TXAPA9; ISSN: 0041-008X
PB Academic Press
DT Journal
LA English
CC 4-3 (Toxicology)
Section cross-reference(s): 18
AB Selected dietary lipids may increase the atherogenic effects of environmental chems., such as polychlorinated biphenyls (PCBs), by cross-amplifying mechanisms leading to dysfunction of the vascular endothelium. The authors have shown previously that the .omega.-6 parent fatty acid, **linoleic acid**, or 3,3',4,4'-tetrachlorobiphenyl (PCB 77), an aryl hydrocarbon (Ah) receptor agonist,

independently can cause disruption of endothelial barrier function. Furthermore, cellular enrichment with **linoleic acid** can amplify PCB-induced endothelial cell dysfunction. The authors hypothesize that the amplified toxicity of **linoleic acid** and PCBs to endothelial cells could be mediated in part by cytotoxic epoxide metabolites of **linoleic acid** called **leukotoxins** (LTX) or their **diol** derivs. (LTXD). Exposure to LTXD resulted in a dose-dependent increase in albumin transfer across endothelial cell monolayers, whereas this disruption of endothelial barrier function was obsd. only at a high concn. of LTX. Pretreatment with the cytosolic epoxide hydrolase inhibitor 1-cyclohexyl-3-dodecyl urea partially protected against the obsd. LTX-induced endothelial dysfunction. Endothelial cell activation mediated by LTX and/or LTXD also enhanced nuclear translocation of the transcription factor NF-.kappa.B and gene expression of the inflammatory cytokine IL-6. Inhibiting cytosolic epoxide hydrolase decreased the LTX-mediated induction of both NF-.kappa.B and the IL-6 gene, whereas the antioxidant vitamin E did not block LTX-induced endothelial cell activation. Most importantly, inhibition of cytosolic epoxide hydrolase blocked both **linoleic acid** -induced cytotoxicity, as well as the additive toxicity of **linoleic acid** plus PCB 77 to endothelial cells. Interestingly, cellular uptake and accumulation of **linoleic acid** was markedly enhanced in the presence of PCB 77. These data suggest that cytotoxic epoxide metabolites of **linoleic acid** play a crit. role in **linoleic acid** -induced endothelial cell dysfunction. Furthermore, the severe toxicity of PCBs in the presence of **linoleic acid** may be due in part to the generation of epoxide and **diol** metabolites. These findings have implications in understanding interactive mechanisms of how dietary fats can modulate dysfunction of the vascular endothelium mediated by certain environmental contaminants. (c) 2001 Academic Press.

ST PCB **linoleic** acid **leukotoxin** toxicity endothelium

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-.kappa.B (nuclear factor .kappa.B); role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT **Blood vessel**
(endothelium; role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Biological transport
(intracellular; role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**leukotoxins**; role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Cytotoxicity
(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Fats and Glyceridic oils, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(role of Me-**linoleic acid** epoxide and **diol**

metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Interleukin 6
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT Biological transport
(uptake; role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT **60-33-3, Linoleic acid**, biological studies
92-52-4D, Biphenyl, chloro derivs. 21019-43-2 32598-13-3, PCB 77 189191-42-2
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

IT 9048-63-9, Epoxide hydrolase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)

RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD

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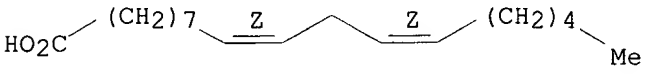
IT **60-33-3, Linoleic acid**, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(role of Me-**linoleic acid** epoxide and **diol** metabolites in the amplified toxicity of **linoleic acid** and polychlorinated biphenyls to vascular endothelial cells)
RN 60-33-3 HCAPLUS
CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L69 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:806272 HCAPLUS
DN 134:173927
TI Toxicity of **linoleic** acid metabolites
AU Greene, Jessica F.; **Hammock, Bruce D.**
CS Departments of Entomology and Environmental Toxicology, University of California at Davis, Davis, CA, 95616, USA
SO Advances in Experimental Medicine and Biology (1999), 469(Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation, and Radiation Injury, 4), 471-477
CODEN: AEMBAP; ISSN: 0065-2598
PB Kluwer Academic/Plenum Publishers
DT Journal; General Review
LA English
CC 4-0 (Toxicology)
AB A review with 22 refs. on the formation of **linoleic acid**

metabolites, synthesis of **leukotoxin** and isoleukotoxin, toxicity of **leukotoxin** and isoleukotoxin, and metabolite toxicity (**leukotoxin diol** and isoleukotoxin **diol**).
ST review toxicity **linoleic** acid metabolite **leukotoxin** isoleukotoxin
IT Toxins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**leukotoxins**; toxicity of **linoleic** acid metabolites)
IT Toxicity
(toxicity of **linoleic** acid metabolites)
IT **60-33-3D**, **Linoleic** acid, metabolites 126639-26-7, Isoleukotoxin
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(toxicity of **linoleic** acid metabolites)
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
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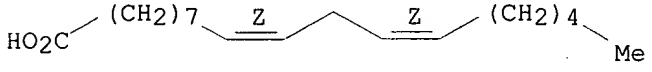
IT **60-33-3D**, **Linoleic** acid, metabolites
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(toxicity of **linoleic** acid metabolites)
RN 60-33-3 HCAPLUS
CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L69 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:545956 HCAPLUS
DN **133:360357**
TI **Linoleic Acid Diols** Are Novel Substrates for

Human UDP-Glucuronosyltransferases
AU Jude, Anthony R.; Little, Joanna M.; Freeman, John P.; Evans, James E.; Radominska-Pandya, Anna; Grant, David F.
CS Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA
SO Archives of Biochemistry and Biophysics (2000), 380(2), 294-302
CODEN: ABBIA4; ISSN: 0003-9861
PB Academic Press
DT Journal
LA English
CC 7-3 (Enzymes)
Section cross-reference(s): 13
AB **Linoleic acid diol glucuronides** have been isolated previously from **urine** of patients suffering from generalized peroxisomal disorders. **Glucuronidation** of **linoleic acid** and **linoleic acid diols** by human liver microsomes was studied to investigate the role of **glucuronide conjugation** in the metab. of **linoleic acid diols**. **Glucuronide** products were isolated and analyzed by TLC and HPLC-MS. HPLC-MS showed ions with (m/z) corresponding to singly **glucuronidated linoleic acid diols** while TLC revealed that the **glucuronidation** was at a hydroxyl position. Kinetic anal. gave apparent Km values in the range of 50-200 .mu.M and Vmax rates from 5 to 12 nmol/mg .times. min. These rates are substantially higher than activities seen for most endogenous hydroxylated substrates. **Assays** using each of the four individually purified **linoleic acid diol** enantiomers suggest that **glucuronidation** occurs at only one of the two hydroxyl groups of each enantiomer. These results show for the first time that hydroxylated fatty acids are actively **glucuronidated** by human liver microsomes and suggest that **glucuronidation** may play a significant role in the biotransformation of **linoleic acid diols** in humans. (c) 2000 Academic Press.
ST **linoleate** diol hydroxyl group UDP glucuronosyltransferase glucuronylation; enantiomer **linoleate** UDP glucuronosyltransferase substrate kinetics
IT Enantiomers
Enzyme kinetics
Glucuronylation
Hydroxyl group
Michaelis constant
(**linoleic acid diols** are novel substrates for human UDP-glucuronosyltransferases)
IT 9030-08-4, Uridine diphosphoglucuronosyltransferase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**linoleic acid diols** are novel substrates for human UDP-glucuronosyltransferases)
IT 112-63-0, **Linoleic acid** methyl ester 10547-36-1
17966-13-1 21019-43-2 61949-82-4 **263399-34-4** 263399-35-5
306940-00-1 306940-02-3 306940-08-9 306940-10-3 306940-12-5
306940-14-7 306940-16-9 306940-18-1 306940-20-5 306940-22-7
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(**linoleic acid diols** are novel substrates for human UDP-glucuronosyltransferases)
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
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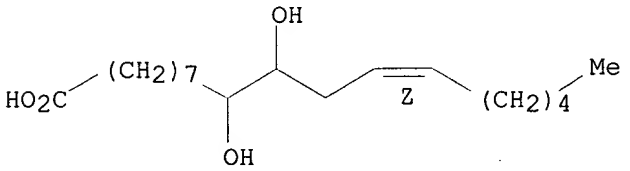
IT **263399-34-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(**linoleic acid diols** are novel substrates for human UDP-glucuronosyltransferases)

RN 263399-34-4 HCAPLUS
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L69 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:259098 HCAPLUS
DN 133:69968
TI Metabolism of Monoepoxides of Methyl **Linoleate**: Bioactivation and Detoxification
AU Greene, Jessica F.; Williamson, Kristin C.; **Newman, John W.**;

Morisseau, Christophe; **Hammock, Bruce D.**
CS Department of Entomology, University of California at Davis, Davis, CA, 95616, USA
SO Archives of Biochemistry and Biophysics (2000), 376(2), 420-432
CODEN: ABBIA4; ISSN: 0003-9861
PB Academic Press
DT Journal
LA English
CC 4-3 (Toxicology)
Section cross-reference(s): 14
AB **Leukotoxin** (ltx) and isoleukotoxin (iltx) Me esters, are metabolites of Me **linoleic acid**, an essential fatty acid. They have been assocd. with **acute respiratory distress syndrome**. The obsd. toxicity of ltx and iltx is, in fact, due to the metab. of the epoxides to their corresponding **diols** by sol. epoxide hydrolase (sEH). Herein, the authors demonstrate that ltx/iltx are toxic in a time-dependent manner to human sEH expressing cells with a LT50 of 10.6 .+-. 0.8 h and that ltx and iltx have KM of 6.15 .+-. 1.0 and 5.17 .+-. 0.56 .mu.M, resp., and Vmax of 2.67 .+-. 0.04 and 1.86 .+-. 0.06 .mu.mol/min/mg, resp., which can be inhibited by sEH inhibitors. The authors show that four major metabolites of ltx/iltx are formed in their system, including ltx/iltx free acid, ltxd/iltxd, free acid, and phosphotidylcholine and phosphotidylethanolamine contg. the carboxylic acid forms of both ltx/iltx and ltxd/iltxd, but that the only metabolite assocd. with toxicity is the carboxylic acid form of ltxd/iltxd, suggesting the involvement of cellular esterases. The authors demonstrate that a serine esterase inhibitor provides some protection from the toxicity of epoxy fatty esters to sEH expressing cells as do intercellular free sulfhydryls, but that this protection is not due to glutathione conjugation. With these data, the authors have proposed an extension of the metabolic pathway for ltx/iltx in eukaryotic cells. (c) 2000 Academic Press.
ST monoepoxide methyl **linoleate** metab bioactivation toxicity detoxification; **leukotoxin diol** epoxide hydrolase phospholipid toxicity detoxication
IT Animal cell line
(Sf-21; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
IT **Respiratory distress syndrome**
(**acute**; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
IT Detoxification
(biol.; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
IT Phosphatidylcholines, biological studies
Phosphatidylethanolamines, biological studies
Phospholipids, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(contg. carboxylic acid forms of both **leukotoxin** and isoleukotoxin and **diols**; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
IT Fatty acids, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(epoxy, esters; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)
IT Epoxides
Epoxides
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)

(fatty alkyl, carboxy, esters; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT Gene, animal
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hsEH; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT Animal cell
(human; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT Toxins
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**leukotoxins, diols**; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT Toxins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**leukotoxins**; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT Epoxides
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**linoleate**; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT Cell death
Cytotoxicity
Enzyme kinetics
Eukaryote (Eukaryotae)
Michaelis constant
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT Thiols (organic), biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 9048-63-9, Epoxide hydrolase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Sol.; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 112-63-0D, Methyl **linoleate**, epoxides
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mono; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 2500-59-6 10547-36-1, Methyl isoleukotoxin 21019-43-2, Methyl **leukotoxin** 126639-25-6, **Leukotoxin** A 126639-26-7, Isoleukotoxin 126639-26-7D, Isoleukotoxin, Me esters
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT **60-33-3D, Linoleic** acid, epoxides, biological studies

RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 73889-55-1, Isoleukotoxin **diol**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 9001-84-7, Phospholipase A2
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 37259-58-8, Serine esterase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 70-18-8, Glutathione, biological studies 65095-03-6
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 70-18-8D, Glutathione, conjugates
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT 141-05-9, Diethyl maleate 92614-59-0, Glutathione ethyl ester
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(protection of cells; monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

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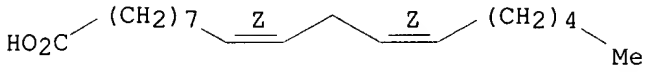
IT **60-33-3D**, **Linoleic** acid, epoxides, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

RN 60-33-3 HCAPLUS
CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L69 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:186660 HCAPLUS
DN 133:70547
TI Identification of CYP2C9 as a Human Liver Microsomal **Linoleic** Acid Epoxygenase
AU Draper, Alison J.; **Hammock, Bruce D.**
CS Department of Chemistry, Bucknell University, Lewisburg, PA, 17837, USA
SO Archives of Biochemistry and Biophysics (2000), 376(1), 199-205
CODEN: ABBIA4; ISSN: 0003-9861
PB Academic Press
DT Journal
LA English
CC 7-3 (Enzymes)
Section cross-reference(s): 15
AB **Leukotoxin** (9,10-epoxy-12-octadecanoate) and isoleukotoxin (12,13-epoxy-9-octadecenoate) are monoepoxides of **linoleic acid**, synthesized by a cytochrome P 450 monooxygenase and possibly by an oxidative burst of inflammatory cells. Recent expts. in this lab. have indicated that the toxicity of **leukotoxin** and isoleukotoxin is not due to these epoxides, but to the 9,10- and 12,13-**diol** metabolites. **Leukotoxin** and isoleukotoxin are metabolized primarily by the sol. epoxide hydrolase to form **leukotoxin diol**. Investigations with recombinant cytochrome P 450 enzymes have demonstrated that **leukotoxin** and isoleukotoxin can be formed by these enzymes. This study used a combination of exptl. approaches to identify the major cytochrome P 450 enzyme in human liver involved in **linoleic acid** epoxidn. The kinetic paramenters were detd.; the Km of **linoleic acid** epoxidn. by pooled human liver microsomes was 170 .mu.M and the Vmax was 58 pmol/mg/min. Correlation anal. was performed using individual samples of human liver microsomes, and the best correlation of **linoleic acid** epoxidn. activity was with tolbutamide hydroxylase activity, CYP2C9. Recombinant CYP2C9 was the most active in **linoleic acid** epoxygenation, and antibody and chem. inhibition also indicated the importance of CYP2C9. This enzyme, therefore, may serve as a therapeutic target in the treatment of inflammation in order to reduce the amt. of circulating **leukotoxin**/isoleukotoxin and their related **diols**. (c) 2000 Academic Press.
ST cytochrome P450 isoenzyme **linoleate** epoxidn human
IT Epoxidation
Michaelis constant
(identification of CYP2C9 as a human liver microsomal **linoleic** acid epoxygenase)
IT 9035-51-2, Cytochrome P450, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(CYP2C9; identification of CYP2C9 as a human liver microsomal **linoleic** acid epoxygenase)
IT 9048-63-9, Epoxide hydrolase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(identification of CYP2C9 as a human liver microsomal **linoleic** acid epoxygenase)
IT **60-33-3, Linoleic** Acid, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(identification of CYP2C9 as a human liver microsomal **linoleic** acid epoxygenase)

IT 73889-55-1, Isoleukotoxin **diol** 126639-25-6, **Leukotoxin** 126639-26-7, Isoleukotoxin **189191-41-1, Leukotoxin diol**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(identification of CYP2C9 as a human liver microsomal **linoleic acid** epoxygenase)

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD

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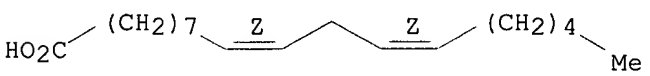
IT **60-33-3, Linoleic** Acid, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(identification of CYP2C9 as a human liver microsomal **linoleic** acid epoxygenase)

RN 60-33-3 HCAPLUS
CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

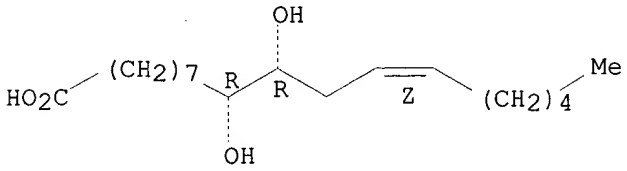
Double bond geometry as shown.



IT **189191-41-1, Leukotoxin diol**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(identification of CYP2C9 as a human liver microsomal **linoleic**

acid epoxygenase)
RN 189191-41-1 HCAPLUS
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L69 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:158286 HCAPLUS
DN 132:318745
TI Toxicity of Epoxy Fatty Acids and Related Compounds to Cells Expressing Human Soluble Epoxide Hydrolase
AU Greene, Jessica F.; **Newman, John W.**; Williamson, Kristin C.; **Hammock, Bruce D.**
CS Department of Entomology, University of California at Davis, Davis, CA, 95616, USA
SO Chemical Research in Toxicology (2000), 13(4), 217-226
CODEN: CRTOEC; ISSN: 0893-228X
PB American Chemical Society
DT Journal
LA English
CC 4-3 (Toxicology)
AB Sol. epoxide hydrolase (sEH) is suggested to alter the mode of action and increase the toxic potency of fatty acid epoxides. To characterize the structural features necessary for sEH-dependent epoxy fatty acid toxicity, 75 aliph. compds. were **assayed** for cytotoxicity in the presence and absence of sEH. Three groups of aliph. epoxide-**diol** pairs were described by their obsd. differential toxicity. Group I compds. were typified by terminal epoxides whose toxicity was reduced in the presence of sEH. Group II compds. were toxic in either their epoxide or **diol** form, but toxicity was unaffected by sEH. Group III compds. exhibited sEH-dependent toxicity and were therefore used to investigate the structural elements required for cytotoxicity in this study. The optimal structure for group III compds. appeared to be a fatty acid 18-20 atoms long (e.g., a carbon backbone plus a terminal heteroatom) with an epoxide positioned between C-7 and C-12. In the absence of sEH, replacement of epoxides with a vicinal **diol** was required for toxicity. While **diol** stereochem. was unimportant, vicinal **diol**-induced toxicity exhibited fewer positional constraints to toxicity than sEH-dependent epoxide toxicity. Tested fatty acids and esters with neither an epoxide nor a vicinal **diol** were not toxic. These data support the hypothesis that long-chain epoxy fatty acid Me esters are potential pro-toxins metabolized by sEH to more toxic **diols**. Furthermore, our results suggest that the endogenous compds., **leukotoxin** Me ester, 9,10(Z)-epoxyoctadec-12(Z)-enoic acid Me ester, and isoleukotoxin Me ester, 12,13(Z)-epoxyoctadec-9(Z)-enoic acid Me ester, are structurally optimized to elicit the obsd. effect.
ST cytotoxicity epoxy fatty acid epoxide hydrolase
IT Structure-activity relationship
(cytotoxic; toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)
IT Mass spectra

(electrospray ionization; toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

IT Fatty acids, biological studies
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(epoxy; toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

IT Epoxides
Epoxides
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(fatty alkyl, carboxy; toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

IT Cytotoxicity
Electron ionization mass spectra
NMR spectroscopy
Spodoptera frugiperda
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

IT 2391-05-1 2566-91-8 2779-85-3 3639-31-4 14936-76-6 17966-13-1
24560-98-3 29714-26-9 34724-39-5 54635-17-5 54635-18-6
56687-67-3 61117-79-1 61140-93-0 61177-05-7 70080-20-5
70116-78-8 73889-55-1 77705-40-9 93635-22-4 99147-53-2
141724-83-6 152175-57-0 182344-96-3 **189191-41-1**
265975-94-8 265975-98-2 265976-01-0 265976-08-7 265976-10-1
265976-15-6 265976-30-5 265976-31-6 265976-32-7 265976-33-8
265976-34-9 265976-35-0 265976-36-1 265976-37-2 265976-38-3
265976-40-7
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

IT 1041-25-4 6088-36-4 6088-42-2 10547-36-1 21019-43-2 22663-09-8
52126-87-1 172995-07-2 189191-42-2 265976-22-5 265976-24-7
265976-26-9 265976-27-0 265976-39-4
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

IT 9048-63-9, Epoxide hydrolase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD

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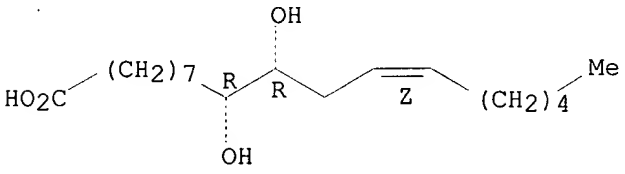
IT **189191-41-1**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)

RN 189191-41-1 HCAPLUS

CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L69 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:110452 HCAPLUS
DN 132:318802
TI **Leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP
AU Totani, Y.; Saito, Y.; Ishizaki, T.; Sasaki, F.; Ameshima, S.; Miyamori, I.
CS Third Dept of Internal Medicine, Fukui Medical University, Fukui, 910-11, Japan
SO European Respiratory Journal (2000), 15(1), 75-79
CODEN: ERJOEI; ISSN: 0903-1936
PB Munksgaard International Publishers Ltd.
DT Journal
LA English
CC 4-5 (Toxicology)
Section cross-reference(s): 14
AB When injected into animals, **leukotoxin** (Lx) causes acute lung injury which is assocd. with neutrophils infiltrating the lung tissues. However, the effect of Lx on neutrophils is still unknown, and recently it has been reported that Lx **diol**, a hydrolyzed metabolite, should be more potent than Lx in vitro. In this study, the authors examd. the

effect of Lx and its **diol** on human neutrophils by assessing their chemotactic response, expression of adhesion mols., and prodn. of peroxides. Both Lx and its **diol** induced chemotaxis in human neutrophils via an involvement of pertussis toxin-sensitive G-proteins, but they did not influence the expression of adhesion mols. or the prodn. of peroxides. Furthermore, Lx synergistically affected chemotaxis with N-formyl-methionyl-leucyl-phenylalanine (fMLP), but not with endothelin 1. Neutrophil chemotaxis induced by both Lx and its **diol** was inhibited by phosphatidylinositol 3-kinase (PI3-K) inhibitors, but not by protein tyrosine kinase (PTK) inhibitors or by protein kinase C (PKC) inhibitors, whereas fMLP-induced chemotaxis was inhibited by PTK inhibitors, but not by PI3-K inhibitors or by PKC inhibitors. These results suggest that neutrophil chemotaxis induced by both Lx and its **diol** involves pathways different from those induced by fMLP. In conclusion, both **leukotoxin** and its **diol** metabolite induce chemotaxis in human neutrophils in an unique way and may act as important bioactive lipids when considering the pathol. mechanism of acute lung injury.

ST **leukotoxin diol** neutrophil chemotaxis signal transduction fMLP

IT Integrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antigens CD11b; **leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT Lung, disease
(injury; **leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT Chemotaxis
Neutrophil
Signal transduction, biological
(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT Peroxides, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT G proteins (guanine nucleotide-binding proteins)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pertussis toxin-sensitive; **leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT Integrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.2; **leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT 113972-57-9 **189191-41-1, Leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

IT 59880-97-6 80449-02-1, Protein tyrosine kinase 115926-52-8, Phosphatidylinositol 3-kinase 123626-67-5, Endothelin 1 141436-78-4, Protein kinase C
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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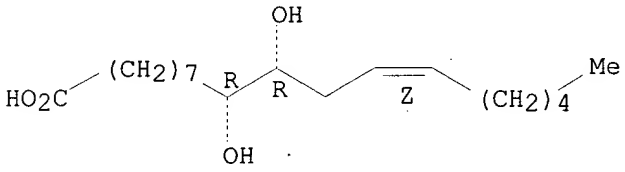
IT **189191-41-1, Leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**leukotoxin** and its **diol** induce neutrophil chemotaxis through signal transduction different from that of fMLP)

RN 189191-41-1 HCAPLUS

CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L69 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:503921 HCAPLUS
DN 131:280999
TI Potent urea and carbamate inhibitors of soluble epoxide hydrolases
AU Morisseau, Christophe; Goodrow, Marvin H.; Dowdy, Deanna; Zheng, Jiang; Greene, Jessica F.; Sanborn, James R.; **Hammock, Bruce D.**
CS Department of Entomology, University of California, Davis, CA, 95616, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1999), 96(16), 8849-8854
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 7, 25

AB The sol. epoxide hydrolase (sEH) plays a significant role in the biosynthesis of inflammation mediators as well as xenobiotic transformations. Herein, the authors report the discovery of substituted ureas and carbamates as potent inhibitors of sEH. Some of these selective, competitive tight-binding inhibitors with nanomolar Ki values interacted stoichiometrically with the homogeneous recombinant murine and human sEHs. These inhibitors enhance cytotoxicity of trans-stilbene oxide, which is active as the epoxide, but reduce cytotoxicity of **leukotoxin**, which is activated by epoxide hydrolase to its toxic

diol. They also reduce toxicity of **leukotoxin** in vivo in mice and prevent symptoms suggestive of **acute respiratory distress syndrome**. These potent inhibitors may be valuable tools for testing hypotheses of involvement of **diol** and epoxide lipids in chem. mediation in vitro or in vivo systems.

ST epoxide hydrolase inhibitor urea carbamate structure

IT **Respiratory distress syndrome**
(**adult, acute**; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT Lipids, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(diol and epoxide; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT Structure-activity relationship
(enzyme-inhibiting, epoxide hydrolases-inhibiting; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT Toxins
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**leukotoxins**, cytotoxicity; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of **diol** and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT Enzyme kinetics
(of inhibition; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 1439-07-2, trans-Stilbene oxide
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cytotoxicity; potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 246165-79-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 57-13-6, Urea, biological studies 64-10-8, N-Phenylurea 102-04-5 102-06-7, N,N'-Diphenylguanidine 102-09-0 538-75-0, Dicyclohexylcarbodiimide 603-54-3 611-92-7 612-01-1 623-95-0, N,N'-Dipropylurea 722-01-0 1212-29-9, N,N'-Dicyclohexylthiourea 2387-23-7, N,N'-Dicyclohexylurea 4559-87-9 13074-28-7 20258-07-5 31510-11-9 36102-06-4 82389-34-2 246165-77-5
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

(Uses)
(potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 9048-63-9, Epoxide hydrolase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

IT 2038-57-5, Benzenepropanamine 3173-53-3, Cyclohexylisocyanate
RL: RCT (Reactant); RACT (Reactant or reagent)
(potent urea and carbamate inhibitors of sol. epoxide hydrolases in relation to structure and role of diol and epoxide lipids and treatment of **acute respiratory distress syndrome**)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L69 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:394294 HCAPLUS
DN 131:168305
TI Effects of **linoleic** acid metabolites on electrical activity in adult rat ventricular myocytes
AU Stimers, Joseph R.; Dobretsov, Maxim; Hastings, Stephanie L.; Jude, Anthony R.; Grant, David F.
CS Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

SO Biochimica et Biophysica Acta (1999), 1438(3), 359-368
CODEN: BBACAQ; ISSN: 0006-3002
PB Elsevier Science B.V.
DT Journal
LA English
CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 14

AB **Leukotoxin** (Lx), an epoxide deriv. of **linoleic acid**, has been suggested to be a toxic mediator of multiple organ failure in burn patients and of **acute respiratory distress syndrome**. Lx prodn. was recently shown during myocardial ischemia/reperfusion. However, a recent study suggested that to be toxic Lx must be metabolized to Lx-**diol**. In the present study, isolated **adult** rat ventricular myocytes were studied with the whole-cell patch-clamp technique to det. the effects of these compds. on cardiac elec. activity. Measurements of action potentials showed that neither **linoleic acid** nor Lx (100 .mu.M) caused any significant changes in action potential properties. However, Lx-**diol** in the range of 10-100 .mu.M produced a dose dependent increase in duration and a decrease in overshoot of the action potential. Subsequent voltage clamp expts. isolating Na current (INa) and transient outward K current (Ito) revealed that Lx-**diol** inhibited INa and Ito by about 80% at 100 .mu.M, while **linoleic acid** and Lx had no effect on these currents at the same concn. While Lx-**diol** produced the same inhibition of INa and Ito at 100 .mu.M, its effects were more potent on Ito with significant inhibition at 10 .mu.M. Lx-**diol** also hastened the activation kinetics of Ito but not INa. The action of Lx-**diol** was rapid (reaching steady state in 3-5 min) and was reversible in 5-10 min following washout. Thus, Lx-**diol** could favor arrhythmias or cardiac arrest in intact heart and may be responsible for the cardiac problems seen in systemic inflammatory response **syndrome**. These results further support the suggestion that Lx is not toxic in the heart but rather must be metabolized to Lx-**diol** to produce toxic effects on cardiac muscle.

ST **linoleate** metabolite **leukotoxin diol** toxic effect heart

IT **Heart, disease**
(arrest; toxic effect of **leukotoxin-diol** on elec. activity of adult rat ventricular myocytes in relation to arrhythmias or cardiac arrest)

IT **Heart, disease**
(arrhythmia; toxic effect of **leukotoxin-diol** on elec. activity of adult rat ventricular myocytes in relation to arrhythmias or cardiac arrest)

IT Electric potential
(biol., action; effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)

IT **Heart**
(elec. activity; effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**leukotoxins**; effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)

IT Biological transport
(potassium; effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)

IT Biological transport
(sodium; effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)

IT **Heart**
(ventricle, myocyte; effects of **linoleic** acid metabolites on

elec. activity in adult rat ventricular myocytes)
IT **189191-41-1, Leukotoxin-diol**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(effects of **linoleic acid** metabolites on elec.
activity in adult rat ventricular myocytes)
IT **60-33-3**, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)
IT 7440-09-7, Potassium, biological studies 7440-23-5, Sodium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)
IT 7440-09-7, Potassium, biological studies 7440-23-5, Sodium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; effects of **linoleic** acid metabolites on elec.
activity in adult rat ventricular myocytes)
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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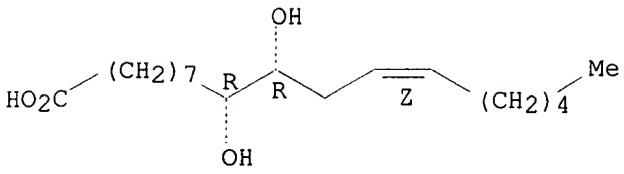
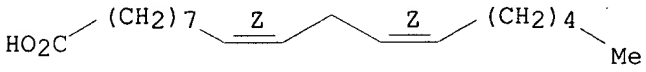
IT **189191-41-1, Leukotoxin-diol**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(effects of **linoleic acid** metabolites on elec.
activity in adult rat ventricular myocytes)
RN 189191-41-1 HCAPLUS
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



IT **60-33-3**, 9,12-Octadecadienoic acid (9Z,12Z)-, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects of **linoleic** acid metabolites on elec. activity in adult rat ventricular myocytes)
RN 60-33-3 HCAPLUS
CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



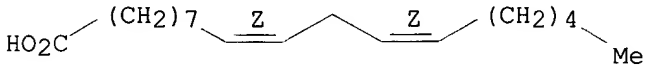
L69 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:478976 HCAPLUS
DN **129:119888**
TI Sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic
IN Bursten, Stuart L.; Federighi, David A.
PA Cell Therapeutics, Inc., USA
SO U.S., 27 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM G01N033-53
NCL 435007100
CC **9-16** (Biochemical Methods)
Section cross-reference(s): 14, 15
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5780237	A	19980714	US 1994-321483	19941012

AB There is disclosed a diagnostic assay for adult respiratory distress syndrome (ARDS), sepsis, multiple organ dysfunction (MOD) and systemic inflammatory response syndrome (SIRS), comprising (a) measuring the amt. of selected unsatd. free fatty acids (FFAs) and satd. FFAs in a body fluid, and (b) detg. a ratio value comprising the sum of the unsatd. FFAs divided by the sum of the satd. FFAs. There is further disclosed a diagnostic assay for ARDS, sepsis, MOD and SIRS, comprising (a) measuring the amt. of 9- or 13-hydroxyoctadecadienoic acid (HODE) and 5-hydroxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HETE) in a body fluid, and (b) detg. a ratio value of HETE and HODE.
ST sepsis respiration distress syndrome inflammatory diagnostic
IT Fatty acids, analysis
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(Satd. free; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
IT **Respiratory distress syndrome**
(**adult**; sepsis, **adult** respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)

IT Organ, animal
(dysfunction, multiple; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
IT Blood analysis
Body fluid
Diagnosis
Gas chromatography
HPLC
Immunoassay
Saliva
Sepsis
Sweat
TLC (thin layer chromatography)
Tear (ocular fluid)
Urine analysis
(sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
IT Antibodies
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
IT Inflammation
(systemic inflammatory response syndrome; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
IT **Fatty acids, analysis**
RL: **ANT (Analyte)**; THU (Therapeutic use); **ANST (Analytical study)**; BIOL (Biological study); USES (Uses)
(**unsatd.**, free; sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
IT 57-10-3, Hexadecanoic acid, analysis 57-11-4, Octadecanoic acid, analysis **60-33-3**, 9,12-Octadecadienoic acid (Z,Z)-, analysis 112-80-1, 9-Octadecenoic acid (Z)-, analysis 506-32-1 544-63-8, Tetradecanoic acid, analysis 18104-45-5 71030-39-2 98524-19-7
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
IT **60-33-3**, 9,12-Octadecadienoic acid (Z,Z)-, analysis
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(sepsis, adult respiratory distress syndrome, and systemic inflammatory response syndrome diagnostic)
RN 60-33-3 HCAPLUS
CN 9,12-Octadecadienoic acid (9Z,12Z)- (9CI) (CA INDEX NAME)

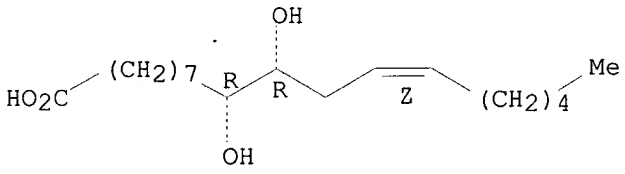
Double bond geometry as shown.



L69 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:365437 HCAPLUS
DN 129:36394
TI In vitro biological effects of **leukotoxin** and **leukotoxin diols** on neutrophil
AU Totani, Yoshitaka; Saito, Yuji; Sasaki, Fumihiko; Miyamori, Isamu; Ishizaki, Takeshi
CS Third Dep. Intern. Med., Fukui Med. Coll., Japan
SO Therapeutic Research (1998), 19(4), 1123-1126

CODEN: THREEL; ISSN: 0289-8020
PB Raifu Saiensu Shuppan K.K.
DT Journal
LA Japanese
CC 1-12 (Pharmacology)
Section cross-reference(s): 14
AB **Leukotoxin** and **leukotoxin diols** increased neutrophil chemotaxis but did not affect the expression of adhesion mols. and peroxide prodn. by neutrophil.
ST **leukotoxin diol** neutrophil chemotaxis
IT Chemotaxis
Neutrophil
(In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)
IT Cell adhesion molecules
Peroxides, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)
IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**leukotoxins**; In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)
IT **189191-41-1, Leukotoxin diol**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)
IT **189191-41-1, Leukotoxin diol**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(In vitro biol. effects of **leukotoxin** and **leukotoxin diols** on neutrophil)
RN 189191-41-1 HCAPLUS
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L69 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:123974 HCAPLUS
DN **128:201056**
TI Methods of treating **adult respiratory distress syndrome** and other inflammatory diseases mediated by polyunsaturated lipid metabolites, and **assays** for epoxide hydrolase inhibitors
IN **Hammock, Bruce D.**; Moghaddam, Mehran F.; Cheek, Jeffrey M.; Borhan, Babak; Fergusson, James; Grant, David F.; Greene, Jessica F.; Matoba, Kazu; Zheng, Jiang; Sisemore, Marlene F.
PA Regents of the University of California, USA
SO PCT Int. Appl., 54 pp.

CODEN: PIXXD2
DT Patent
LA English
IC ICM A01N033-02
ICS A01N043-20; A01N043-24; A01N037-02; A61K031-13; A61K031-23; A61K031-335
CC 1-7 (Pharmacology)
Section cross-reference(s): 7
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9806261	A1	19980219	WO 1997-US14385	19970813
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5955496	A	19990921	US 1997-909523	19970812
AU 9740692	A1	19980306	AU 1997-40692	19970813
EP 926951	A1	19990707	EP 1997-938335	19970813
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6174695	B1	20010116	US 1999-312207	19990514
PRAI US 1996-23397P	P	19960813		
US 1997-909523	A	19970812		
WO 1997-US14385	W	19970813		

AB Methods are provided for treating inflammatory diseases mediated by polyunsatd. lipid metabolites by inhibiting epoxide hydrolase. The methods may be used for treating e.g. **adult respiratory distress syndrome**. Also provided are methods for **assaying** or screening the epoxide hydrolase inhibitors for inhibitory specificity and for toxicity, as well as novel biol. active THF diols of arachidonic acid, including antibodies thereto.

ST inflammatory disease treatment epoxide hydrolase inhibitor; polyunsatd lipid metabolite inflammatory disease; screening epoxide hydrolase inhibitor inflammation; **ARDS** epoxide hydrolase inhibitor

IT **Respiratory distress syndrome**
(**adult**; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Lipids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(alkoxides; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Lung
(alveolus, epithelium, cells; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Nucleic acids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antisense; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Insect (Insecta)
(cell line; epoxide hydrolase inhibitors, and screening thereof, for

treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(dihydroxy-; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Imides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diimides, lipophilic; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT **Immunoassay**
(enzyme-linked immunosorbent **assay**; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Animal tissue culture
Anti-inflammatory agents
Biological transport
Drug screening
Spodoptera frugiperda
Structure-activity relationship
(epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Biological transport
(influx, calcium; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Baculoviridae
(insect cell line transfected with; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Skin
(keratinocyte; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Toxins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**leukotoxins**, metabolites; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT Antibodies
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(to arachidonate THF diol metabolites; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT 6088-36-4, Methyl isoleukotoxin diol 73889-55-1, Isoleukotoxin diol **189191-41-1, Leukotoxin diol** 189191-42-2, Methyl **leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT 112-63-0, Methyl **linoleate** 10547-36-1, Methyl isoleukotoxin

21019-43-2, Methyl **leukotoxin** 126639-26-7, Isoleukotoxin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT 112-63-0D, Methyl **linoleate**, diepoxides 538-75-0, Dicyclohexylcarbodiimide 1885-07-0D, derivs. 5411-12-1 5411-12-1D, Chalcone oxide, derivs. 5633-36-3 6969-02-4 29425-81-8 32046-97-2 32753-95-0 40327-51-3 40327-54-6 40327-57-9 40327-58-0 42846-54-8 51477-11-3 203925-63-7 203925-64-8 203925-65-9 203925-66-0 203925-67-1 203925-68-2 203925-69-3 203925-70-6 203925-71-7 203925-72-8 203925-73-9 203925-74-0 203925-75-1 203925-76-2 203925-77-3 203925-78-4 203925-79-5 203925-80-8 203925-81-9 203925-82-0 203925-83-1 203925-84-2 203925-85-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT 9048-63-9, Epoxide hydrolase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT 506-32-1D, Arachidonic acid, THF diols
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

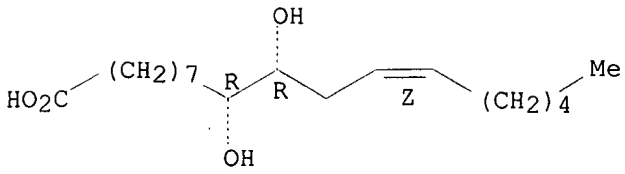
IT 7440-70-2, Calcium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(intracellular; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT 506-32-1, Arachidonic acid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolites; epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

IT **189191-41-1, Leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

RN 189191-41-1 HCAPLUS
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

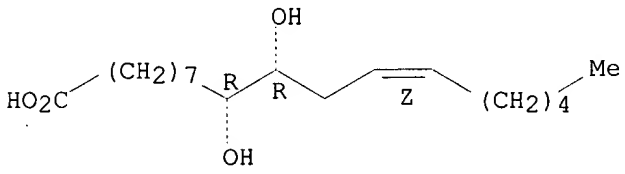
Relative stereochemistry.
Double bond geometry as shown.



L69 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:297665 HCAPLUS
DN 126:289133
TI Bioactivation of **leukotoxins** to their toxic **diols** by epoxide hydrolase
AU Moghaddam, Mehran F.; Grant, David F.; Cheek, Jeffrey M.; Greene, Jessica F.; Williamson, Kristin C.; **Hammock, Bruce D.**
CS Environ. Stud., DuPont Agric. Pro., Exp. Stn., Wilmington, DE, 19880-0402, USA
SO Nat. Med. (N. Y.) (1997), 3(5), 562-566
CODEN: NAMEFI; ISSN: 1078-8956
PB Nature Publishing Co.
DT Journal
LA English
CC 4-3 (Toxicology)
AB **Leukotoxin** is a **linoleic acid** oxide produced by leukocytes and has been assocd. with the multiple organ failure and **adult respiratory distress syndrome** seen in some severe burn patients. **Leukotoxin** has been reported to be toxic when injected into animals i.v. Herein, the authors report that this lipid is not directly cytotoxic in at least two in vitro systems. Using a baculovirus expression system the authors demonstrate that **leukotoxin** is only cytotoxic in the presence of epoxide hydrolases. In addn., it is the **diol** metabolite that proves toxic to pulmonary alveolar epithelial cells, suggesting a crit. role for the **diol** in **leukotoxin**-assocd. **respiratory** disease. In vivo data also support the toxicity of **leukotoxin diol**. For the first time the authors demonstrate that sol. epoxide hydrolase can bioactivate epoxides to **diols** that are apparently cytotoxic. Thus, **leukotoxin** should be regarded as a protoxin corresponding to the more toxic **diol**. This clearly has implications for designing new clin. interventions.
ST **leukotoxin** bioactivation **diol** epoxide hydrolase
IT Alveolar epithelium (lung)
HeLa cell
Respiratory tract diseases
Spodoptera frugiperda
(bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT 6088-36-4, Methyl isoleukotoxin **diol**
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(Me isoleukotoxin **diol**; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT 10547-36-1, Methyl isoleukotoxin
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(Me isoleukotoxin; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT 189191-42-2, Methyl **leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(Me **leukotoxin diol**; bioactivation of

leukotoxins to toxic **diols** by epoxide hydrolase)
IT 149405-48-1, Methyl **leukotoxin**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(Me **leukotoxin**; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT 112-63-0, Methyl **linoleate**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT 61949-82-4
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT 9048-63-9, Epoxide hydrolase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT 73889-55-1, Isoleukotoxin **diol**
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(isoleukotoxin **diol**; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT 126639-26-7, Isoleukotoxin
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(isoleukotoxin; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT **189191-41-1, Leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**leukotoxin diol**; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT **189191-41-1, Leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**leukotoxin diol**; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
RN 189191-41-1 HCAPLUS
CN 12-Octadecenoic acid, 9,10-dihydroxy-, (9R,10R,12Z)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L69 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:161958 HCAPLUS
TI Study of the mechanism of inhibition of epoxide hydrolases by chalcone oxides.
AU Morisseau, C.; Du, G.; **Newman, J. W.**; Nakagawa, Y.; Zheng, J.; **Hammock, B. D.**
CS Departments Entomology and Environmental Toxicology, University

California, Davis, CA, 95616, USA
SO Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (1997), MEDI-126 Publisher: American Chemical Society, Washington, D. C. CODEN: 64AOAA
DT Conference; Meeting Abstract
LA English
AB Metab. of drugs and xenobiotics is among the important factors in detg. the biol. and toxicol. effects of exposure. Many mutagens and carcinogens are degraded by the sol. and microsomal epoxide hydrolases. Conversely, the **diol** resulting from the hydrolysis of **leukotoxin** by an epoxide hydrolase is the metabolite responsible for the toxicity of this compd. in cell culture. If prodn. of **leukotoxin** **diol** results in the clin. symptoms of **ARDS**, inhibition of the epoxide hydrolase could reduce symptoms. In this study, we report (1) the quant. anal. of the structure-activity relationship for about forty inhibitors (chalcone oxide derivs.) of sol. epoxide hydrolases, (2) the kinetic study of their action, and (3) the detn. of the structure of the enzyme-inhibitor complex. These results provide an understanding of the mechanism of inhibition permitting the design of therapeutic drug or pro-drug for the treatment of **ARDS**.

=> fil reg
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DICTIONARY FILE UPDATES: 19 JUN 2002 HIGHEST RN 432491-02-6

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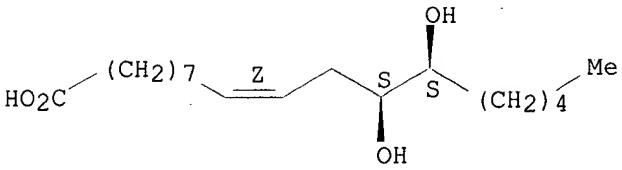
Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d l71 ide can

L71 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **73889-55-1** REGISTRY
CN 9-Octadecenoic acid, 12,13-dihydroxy-, (9Z,12R,13R)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 9-Octadecenoic acid, 12,13-dihydroxy-, [R*,R*-(Z)]-
OTHER NAMES:
CN Isoleukotoxin diol
FS STEREOSEARCH
DR 59981-82-7
MF C18 H34 O4
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

12 REFERENCES IN FILE CA (1967 TO DATE)
12 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:39307

REFERENCE 2: 133:70547

REFERENCE 3: 133:69968

REFERENCE 4: 132:318745

REFERENCE 5: 128:201056

REFERENCE 6: 127:230447

REFERENCE 7: 126:289133

REFERENCE 8: 124:226704

REFERENCE 9: 110:172676

REFERENCE 10: 103:140570

=> d his l71-

(FILE 'REGISTRY' ENTERED AT 17:05:40 ON 21 JUN 2002)

FILE 'REGISTRY' ENTERED AT 17:05:59 ON 21 JUN 2002

FILE 'HCAPLUS' ENTERED AT 17:06:08 ON 21 JUN 2002

FILE 'REGISTRY' ENTERED AT 17:07:30 ON 21 JUN 2002
L71 1 S 73889-55-1

FILE 'HCAPLUS' ENTERED AT 17:07:40 ON 21 JUN 2002
L72 13 S L71
L73 5 S L72 AND L12-L16
L74 1 S L72 AND L18-L29
L75 5 S L73,L74 AND L69
L76 8 S L72 NOT L75

FILE 'REGISTRY' ENTERED AT 17:08:58 ON 21 JUN 2002

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FILE 'HCAPLUS' ENTERED AT 17:09:11 ON 21 JUN 2002

FILE COVERS 1907 - 21 Jun 2002 VOL 136 ISS 25
FILE LAST UPDATED: 19 Jun 2002 (20020619/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d l75 bib abs hitrn tot

L75 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:259098 HCAPLUS
DN 133:69968
TI Metabolism of Monoepoxides of Methyl **Linoleate**: Bioactivation and Detoxification
AU Greene, Jessica F.; Williamson, Kristin C.; **Newman, John W.**; Morisseau, Christophe; **Hammock, Bruce D.**
CS Department of Entomology, University of California at Davis, Davis, CA, 95616, USA
SO Archives of Biochemistry and Biophysics (2000), 376(2), 420-432
CODEN: ABBIA4; ISSN: 0003-9861
PB Academic Press
DT Journal
LA English
AB **Leukotoxin** (ltx) and isoleukotoxin (iltx) Me esters, are metabolites of Me **linoleic acid**, an essential fatty acid. They have been assocd. with **acute respiratory distress syndrome**. The obsd. toxicity of ltx and iltx is, in fact, due to the metab. of the epoxides to their corresponding **diols** by sol. epoxide hydrolase (sEH). Herein, the authors demonstrate that ltx/iltx are toxic in a time-dependent manner to human sEH expressing cells with a LT50 of 10.6 .+-. 0.8 h and that ltx and iltx have KM of 6.15 .+-. 1.0 and 5.17 .+-. 0.56 .mu.M, resp., and Vmax of 2.67 .+-. 0.04 and 1.86 .+-. 0.06 .mu.mol/min/mg, resp., which can be inhibited by sEH inhibitors. The authors show that four major metabolites of ltx/iltx are formed in their system, including ltx/iltx free acid, ltxd/iltxd, free acid, and phosphotidylcholine and phosphotidylethanolamine contg. the carboxylic acid forms of both ltx/iltx and ltxd/iltxd, but that the only metabolite assocd. with toxicity is the carboxylic acid form of ltxd/iltxd, suggesting the involvement of cellular esterases. The authors demonstrate that a serine esterase inhibitor provides some protection from the toxicity of epoxy fatty esters to sEH expressing cells as do intercellular free sulfhydryls, but that this protection is not due to glutathione conjugation. With these data, the authors have proposed an extension of the metabolic pathway for ltx/iltx in eukaryotic cells. (c) 2000 Academic Press.
IT **60-33-3D**, **Linoleic** acid, epoxides, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

IT **73889-55-1**, Isoleukotoxin **diol**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(monoepoxides of me **linoleate** metab. and bioactivation and detoxification in relation to **leukotoxin** toxicity)

RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L75 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:186660 HCAPLUS
DN 133:70547
TI Identification of CYP2C9 as a Human Liver Microsomal **Linoleic** Acid Epoxygenase
AU Draper, Alison J.; **Hammock, Bruce D.**
CS Department of Chemistry, Bucknell University, Lewisburg, PA, 17837, USA
SO Archives of Biochemistry and Biophysics (2000), 376(1), 199-205
CODEN: ABBIA4; ISSN: 0003-9861
PB Academic Press
DT Journal
LA English
AB **Leukotoxin** (9,10-epoxy-12-octadecanoate) and isoleukotoxin (12,13-epoxy-9-octadecenoate) are monoepoxides of **linoleic acid**, synthesized by a cytochrome P 450 monooxygenase and possibly by an oxidative burst of inflammatory cells. Recent expts. in this lab. have indicated that the toxicity of **leukotoxin** and isoleukotoxin is not due to these epoxides, but to the 9,10- and 12,13-**diol** metabolites. **Leukotoxin** and isoleukotoxin are metabolized primarily by the sol. epoxide hydrolase to form **leukotoxin diol**. Investigations with recombinant cytochrome P 450 enzymes have demonstrated that **leukotoxin** and isoleukotoxin can be formed by these enzymes. This study used a combination of exptl. approaches to identify the major cytochrome P 450 enzyme in human liver involved in **linoleic acid** epoxidn. The kinetic paramenters were detd.; the Km of **linoleic acid** epoxidn. by pooled human liver microsomes was 170 .mu.M and the Vmax was 58 pmol/mg/min. Correlation anal. was performed using individual samples of human liver microsomes, and the best correlation of **linoleic acid** epoxidn. activity was with tolbutamide hydroxylase activity, CYP2C9. Recombinant CYP2C9 was the most active in **linoleic acid** epoxygenation, and antibody and chem. inhibition also indicated the importance of CYP2C9. This enzyme, therefore, may serve as a therapeutic target in the treatment of inflammation in order to reduce the amt. of circulating **leukotoxin**/isoleukotoxin and their related **diols**. (c) 2000 Academic Press.

IT **60-33-3**, **Linoleic** Acid, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(identification of CYP2C9 as a human liver microsomal **linoleic** acid epoxygenase)

IT **73889-55-1**, Isoleukotoxin **diol** **189191-41-1**, **Leukotoxin diol**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(identification of CYP2C9 as a human liver microsomal **linoleic acid** epoxygenase)

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L75 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:158286 HCAPLUS

DN 132:318745
TI Toxicity of Epoxy Fatty Acids and Related Compounds to Cells Expressing Human Soluble Epoxide Hydrolase
AU Greene, Jessica F.; **Newman, John W.**; Williamson, Kristin C.; **Hammock, Bruce D.**
CS Department of Entomology, University of California at Davis, Davis, CA, 95616, USA
SO Chemical Research in Toxicology (2000), 13(4), 217-226
CODEN: CRTOEC; ISSN: 0893-228X
PB American Chemical Society
DT Journal
LA English
AB Sol. epoxide hydrolase (sEH) is suggested to alter the mode of action and increase the toxic potency of fatty acid epoxides. To characterize the structural features necessary for sEH-dependent epoxy fatty acid toxicity, 75 aliph. compds. were **assayed** for cytotoxicity in the presence and absence of sEH. Three groups of aliph. epoxide-**diol** pairs were described by their obsd. differential toxicity. Group I compds. were typified by terminal epoxides whose toxicity was reduced in the presence of sEH. Group II compds. were toxic in either their epoxide or **diol** form, but toxicity was unaffected by sEH. Group III compds. exhibited sEH-dependent toxicity and were therefore used to investigate the structural elements required for cytotoxicity in this study. The optimal structure for group III compds. appeared to be a fatty acid 18-20 atoms long (e.g., a carbon backbone plus a terminal heteroatom) with an epoxide positioned between C-7 and C-12. In the absence of sEH, replacement of epoxides with a vicinal **diol** was required for toxicity. While **diol** stereochem. was unimportant, vicinal **diol**-induced toxicity exhibited fewer positional constraints to toxicity than sEH-dependent epoxide toxicity. Tested fatty acids and esters with neither an epoxide nor a vicinal **diol** were not toxic. These data support the hypothesis that long-chain epoxy fatty acid Me esters are potential pro-toxins metabolized by sEH to more toxic **diols**. Furthermore, our results suggest that the endogenous compds., **leukotoxin** Me ester, 9,10(Z)-epoxyoctadec-12(Z)-enoic acid Me ester, and isoleukotoxin Me ester, 12,13(Z)-epoxyoctadec-9(Z)-enoic acid Me ester, are structurally optimized to elicit the obsd. effect.
IT **73889-55-1 189191-41-1**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (toxicity of epoxy fatty acids and related compds. to cells expressing human sol. epoxide hydrolase)
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L75 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:123974 HCAPLUS
DN **128:201056**
TI Methods of treating **adult respiratory distress syndrome** and other inflammatory diseases mediated by polyunsaturated lipid metabolites, and **assays** for epoxide hydrolase inhibitors
IN **Hammock, Bruce D.**; Moghaddam, Mehran F.; Cheek, Jeffrey M.; Borhan, Babak; Fergusson, James; Grant, David F.; Greene, Jessica F.; Matoba, Kazu; Zheng, Jiang; Sisemore, Marlene F.
PA Regents of the University of California, USA
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 9806261 A1 19980219 WO 1997-US14385 19970813
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
US 5955496 A 19990921 US 1997-909523 19970812
AU 9740692 A1 19980306 AU 1997-40692 19970813
EP 926951 A1 19990707 EP 1997-938335 19970813
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
US 6174695 B1 20010116 US 1999-312207 19990514
PRAI US 1996-23397P P 19960813
US 1997-909523 A 19970812
WO 1997-US14385 W 19970813

AB Methods are provided for treating inflammatory diseases mediated by polyunsatd. lipid metabolites by inhibiting epoxide hydrolase. The methods may be used for treating e.g. **adult respiratory distress syndrome**. Also provided are methods for **assaying** or screening the epoxide hydrolase inhibitors for inhibitory specificity and for toxicity, as well as novel biol. active THF diols of arachidonic acid, including antibodies thereto.

IT **73889-55-1**, Isoleukotoxin diol **189191-41-1**, **Leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(epoxide hydrolase inhibitors, and screening thereof, for treatment of **ARDS** and other inflammatory diseases mediated by polyunsatd. lipid metabolites)

L75 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:297665 HCAPLUS
DN 126:289133
TI Bioactivation of **leukotoxins** to their toxic **diols** by epoxide hydrolase
AU Moghaddam, Mehran F.; Grant, David F.; Cheek, Jeffrey M.; Greene, Jessica F.; Williamson, Kristin C.; **Hammock, Bruce D.**
CS Environ. Stud., DuPont Agric. Pro., Exp. Stn., Wilmington, DE, 19880-0402, USA
SO Nat. Med. (N. Y.) (1997), 3(5), 562-566
CODEN: NAMEFI; ISSN: 1078-8956
PB Nature Publishing Co.
DT Journal
LA English
AB **Leukotoxin** is a **linoleic acid** oxide produced by leukocytes and has been assocd. with the multiple organ failure and **adult respiratory distress syndrome** seen in some severe burn patients. **Leukotoxin** has been reported to be toxic when injected into animals i.v. Herein, the authors report that this lipid is not directly cytotoxic in at least two in vitro systems. Using a baculovirus expression system the authors demonstrate that **leukotoxin** is only cytotoxic in the presence of epoxide hydrolases. In addn., it is the **diol** metabolite that proves toxic to pulmonary alveolar epithelial cells, suggesting a crit. role for the **diol** in **leukotoxin**-assocd. **respiratory** disease. In vivo data also support the toxicity of **leukotoxin diol**. For the first time the authors demonstrate that sol. epoxide hydrolase can bioactivate epoxides to **diols** that are apparently cytotoxic. Thus, **leukotoxin** should be regarded as a

protoxin corresponding to the more toxic **diol**. This clearly has implications for designing new clin. interventions.
IT **73889-55-1**, Isoleukotoxin **diol**
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(isoleukotoxin **diol**; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)
IT **189191-41-1**, **Leukotoxin diol**
RL: ADV (Adverse effect, including toxicity); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**leukotoxin diol**; bioactivation of **leukotoxins** to toxic **diols** by epoxide hydrolase)

=> fil biosis
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CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 19 June 2002 (20020619/ED)

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L96 ANSWER 1 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:289566 BIOSIS
DN PREV200200289566
TI Effects of linoleic acid metabolites on cardiac Na+ current.
AU Harrell, Maddison D. (1); Stimers, Joseph R.
CS (1) Tulane University, New Orleans, LA USA
SO Biophysical Journal, (January, 2002) Vol. 82, No. 1 Part 2, pp. 87a. http://intl.biophysj.org/. print.
Meeting Info.: 46th Annual Meeting of the Biophysical Society San Francisco, California, USA February 23-27, 2002
ISSN: 0006-3495.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520**
Cytology and Cytochemistry - Animal *02506
Biophysics - Membrane Phenomena *10508
Cardiovascular System - Physiology and Biochemistry *14504
IT Major Concepts
Cardiovascular System (Transport and Circulation); Membranes (Cell Biology)
IT Parts, Structures, & Systems of Organisms
ventricular myocytes: circulatory system
IT Chemicals & Biochemicals
9,10-dihydroxy-12-octadecenoic acid; 9,10-dihydroxy-12-octadecenoic acid ester; 9,10-epoxy-12-octadecenoic acid; 9,10-epoxy-12-octadecenoic acid ester; linoleic acid metabolites
IT Miscellaneous Descriptors
cardiac sodium ion current; Meeting Abstract; Meeting Poster
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN **53734-70-6** (9,10-DIHYDROXY-12-OCTADECENOIC ACID)

L96 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:250820 BIOSIS
DN PREV200100250820
TI Linoleic acid-derived epoxides alter calcium and nitric oxide metabolism in endothelial cells.
AU Saraswathi, V. (1); Narayan, P. (1); **Hammock, B. D.**; Meerarani, P. (1); Toborek, M. (1); Hennig, B. (1)
CS (1) University of Kentucky, Lexington, KY, 40506-0054 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A190. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT **Conference**
LA English
SL English
AB Several lines of evidence suggest that increased intake of linoleic acid (LA), the predominant polyunsaturated fatty acid in Western diets, can cause vascular endothelial cell (EC) activation. The toxic effects of LA may be mediated by its epoxide metabolites **leukotoxin** (LTX) and **leukotoxin diol** (LTXD). Both (Ca2+)i and NO are critical regulators of normal/abnormal functions of the vasculature. We investigated whether LA and its metabolites can modify (Ca2+)i and NO levels in porcine artery EC. LA treatment increased (Ca2+)i after 3 h of exposure. In contrast, LTX or LTXD increased (Ca2+)i within minutes. Similar to the effects on (Ca2+)i, both LTX and its **diol** metabolite increased the formation of NO more rapidly than LA, as observed by an increase in DAF-2 fluorescence. However, the increase in NO was observed later than the rise in (Ca2+)i, thereby suggesting the calcium dependency of eNOS activation. Excessive (Ca2+)i and NO formation may lead to increased oxidative stress. EC exposure to both LA and its epoxide metabolites increased NF-kappaB activation. Our data suggest that LA metabolites contribute markedly to EC activation, possibly mediated through altered (Ca2+)i and NO metabolism and a resulting alterations in EC redox status.
CC Biochemical Studies - Minerals *10069
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General *10060
Biochemical Studies - Lipids *10066
Metabolism - General Metabolism; Metabolic Pathways *13002
Nutrition - General Studies, Nutritional Status and Methods *13202
Cardiovascular System - Physiology and Biochemistry *14504
BC Suidae 85740
IT Major Concepts
Metabolism; Nutrition; Cardiovascular System (Transport and Circulation)
IT Parts, Structures, & Systems of Organisms
vascular endothelial cell: circulatory system, redox status
IT Chemicals & Biochemicals
calcium(II) ion: intracellular, metabolism; fatty acid: metabolism; linoleic acid-derived epoxides; nitric oxide: metabolism
IT Miscellaneous Descriptors
Western diet; Meeting Abstract
ORGN Super Taxa
Suidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
porcine (Suidae)
ORGN Organism Superterms
Animals; Artiodactyls; Chordates; Mammals; Nonhuman Mammals; Nonhuman

Vertebrates; Vertebrates
RN 14127-61-8 (CALCIUM(II) ION)
10102-43-9 (NITRIC OXIDE)

L96 ANSWER 3 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:406235 BIOSIS
DN **PREV199900406235**
TI **Leukotoxins** and the lung.
AU Ishizaki, T. (1); Ozawa, T.; Voelkel, N. F.
CS (1) Department of Internal Medicine, Fukui Medical University, Fukui, 910-11 Japan
SO Pulmonary Pharmacology & Therapeutics, (1999) Vol. 12, No. 3, pp. 145-155. ISSN: 1094-5539.
DT General Review
LA English
CC Toxicology - General; Methods and Experimental *22501
Biochemical Studies - General *10060
Biophysics - General Biophysical Studies *10502
Respiratory System - General; Methods *16001
BC Hominidae 86215
Muridae 86375
IT Major Concepts
Respiratory System (Respiration); Toxicology
IT Parts, Structures, & Systems of Organisms
lung: respiratory system; pulmonary cells: respiratory system; pulmonary vessels: respiratory system
IT Diseases
lung injury: **leukotoxin**-induced, respiratory system disease
IT Chemicals & Biochemicals
eNOS [endothelial nitric oxide synthase]; iNOS [inducible nitric oxide synthase]; **leukotoxin diol**: **leukotoxin** epoxide hydrolase-metabolite; **leukotoxin**: cytotoxicity, linoleate epoxide; oxygen radicals: production; superoxide: production
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); rat (Muridae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates
RN 113972-57-9 (**LEUKOTOXIN**)
189191-41-1 (**LEUKOTOXIN DIOL**)
11062-77-4 (OXYGEN RADICALS)
11062-77-4 (SUPEROXIDE)

L96 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:202955 BIOSIS
DN PREV199800202955
TI **Leukotoxin-diol** produces greater acute lung injury in mice than does **leukotoxin**.
AU Zheng, J.; Plopper, C.; **Hammock, B.**
CS Univ. Calif., Davis, CA 95616 USA
SO FASEB Journal, (March 20, 1998) Vol. 12, No. 5, pp. A787.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 98, Part II San Francisco, California, USA April 18-22, 1998 Federation of American Societies for Experimental Biology . ISSN: 0892-6638.
DT **Conference**
LA English
CC Toxicology - General; Methods and Experimental *22501
Metabolism - General Metabolism; Metabolic Pathways *13002
Respiratory System - Pathology *16006

General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Muridae 86375
IT Major Concepts
Metabolism; Respiratory System (Respiration); Toxicology
IT Diseases
acute lung injury: injury, respiratory system disease
IT Chemicals & Biochemicals
leukotoxin-diol: toxicity; **leukotoxin**: toxicity; linoleic acid
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 113972-57-9 (**LEUKOTOXIN**)
60-33-3 (LINOLEIC ACID)

L96 ANSWER 5 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:125460 BIOSIS
DN **PREV199698697595**
TI Glucuronic acid-conjugated dihydroxy fatty acids in the urine of patients with generalized peroxisomal disorders.
AU Street, Jacqueline M. (1); Evans, James E.; Natowicz, Marvin R.
CS (1) E.K. Shriver Center, 200 Trapelo Rd., Waltham, MA 02254 USA
SO Journal of Biological Chemistry, (1996) Vol. 271, No. 7, pp. 3507-3516. ISSN: 0021-9258.
DT Article
LA English
AB Urine extracts from children diagnosed with generalized peroxisomal disorders were screened by continuous flow-negative ion fast atom bombardment-mass spectrometry. In 45 of 60 children with generalized peroxisomal disorders, we observed one or more intense ions (m/z 489, 505, 461, and others) that are infrequently found in children with cholestatic liver disease or normal children. Compounds giving rise to these ions were isolated using reverse phase and anion exchange chromatography. After appropriate derivatization and/or methanolysis the compounds were analyzed using capillary gas chromatography-mass spectrometry. The major compounds were found to be 12,13-dihydroxy-9-octadecenoic acid and 9,10-dihydroxy-12-octadecenoic acid, with one of the hydroxyl groups in glycosidic linkage with glucuronic acid. Minor compounds were glucuronic acid conjugates of 9,10-dihydroxy-octadecanoic acid, and 12,13-dihydroxy-6,9-, 15,16-dihydroxy-9,12-, and 9,10-dihydroxy-12,15-octadecadienoic acids. A series of hexadecanoic, hexadecenoic, and hexadecadienoic acid glucuronides which appear to be beta-oxidation products of the C18 fatty acids were also observed, with the major species being 10,11-dihydroxy-7-hexadecenoic acid glucuronide. In all, 16 C 16 and C 18 dihydroxy fatty acids were identified by gas chromatography-mass spectrometry. A series of at least 11 trihydroxy fatty acids was also observed but not fully characterized. Measurement of these compounds may prove to be useful in the diagnosis of some peroxisomal disorders.
CC Genetics and Cytogenetics - Human *03508
Clinical Biochemistry; General Methods and Applications *10006
Biochemical Studies - Lipids *10066
Pathology, General and Miscellaneous - Diagnostic *12504
Metabolism - Lipids *13006
Metabolism - Metabolic Disorders *13020
Digestive System - Pathology *14006
Urinary System and External Secretions - Physiology and Biochemistry

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     *15504
BC   Hominidae  *86215
IT   Major Concepts
        Biochemistry and Molecular Biophysics; Clinical Chemistry (Allied
        Medical Sciences); Gastroenterology (Human Medicine, Medical Sciences);
        Genetics; Metabolism; Pathology; Urinary System (Chemical Coordination
        and Homeostasis)
IT   Chemicals & Biochemicals
        GLUCURONIC ACID; 12,13-DIHYDROXY-9-OCTADECENOIC ACID;
        9,10-DIHYDROXY-12-OCTADECENOIC ACID; 9,10-DIHYDROXY-OCTADECANOIC ACID
IT   Miscellaneous Descriptors
        CHILDREN; CHOLESTATIC LIVER DISEASE; DIAGNOSIS; TRIHYDROXY FATTY ACIDS;
        12,13-DIHYDROXY-6,9-OCTADECADIENOIC ACID; 12,13-DIHYDROXY-9-
        OCTADECENOIC ACID; 15,16-DIHYDROXY-9,12-OCTADECADIENOIC ACID;
        9,10-DIHYDROXY-OCTADECANOIC ACID; 9,10-DIHYDROXY-12-OCTADECENOIC ACID;
        9,10-DIHYDROXY-12,15-OCTADECADIENOIC ACID
ORGN Super Taxa
        Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
        human (Hominidae)
ORGN Organism Superterms
        animals; chordates; humans; mammals; primates; vertebrates
RN   576-37-4Q (GLUCURONIC ACID)
     6556-12-3Q (GLUCURONIC ACID)
     53734-71-7 (12,13-DIHYDROXY-9-OCTADECENOIC ACID)
       53734-70-6 (9,10-DIHYDROXY-12-OCTADECENOIC ACID)
     120-87-6 (9,10-DIHYDROXY-OCTADECANOIC ACID)


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    http://www.derwent.com/userguides/dwpi_guide.html <<<

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L110 ANSWER 1 OF 2  WPIX (C) 2002 THOMSON DERWENT
AN   2000-543662 [49]   WPIX
CR   1998-159182 [14]
DNC  C2000-161838
TI   Epoxide hydrolase inhibitors useful for treating inflammation and in
     conjunction with cancer therapy.
DC   B05 C03
IN   GOODROW, M H; HAMMOCK, B D; MORISSEAU, C H; SANBORN, J;
```

SEVERSON, T; ZHENG, J
PA (REGC) UNIV CALIFORNIA
CYC 90
PI WO 2000048593 A1 20000824 (200049)* EN 40p A61K031-317
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000033608 A 20000904 (200103) A61K031-317
EP 1154764 A1 20011121 (200176) EN A61K031-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000048593 A1 WO 2000-US3495 20000210; AU 2000033608 A AU 2000-33608 20000210; EP 1154764 A1 EP 2000-911767 20000210, WO 2000-US3495 20000210
FDT AU 2000033608 A Based on WO 200048593; EP 1154764 A1 Based on WO 200048593
PRAI US 1999-252148 19990218
IC ICM A61K031-00; A61K031-317
AB WO 200048593 A UPAB: 20011227
NOVELTY - Biologically stable inhibitors of soluble epoxide hydrolases used to selectively inhibit epoxide hydrolase in therapeutic and agricultural applications.

DETAILED DESCRIPTION - Treating an epoxide hydrolase, useful to purify, isolate, or inhibit the epoxide hydrolase comprises providing a carbonyl compound of formula (I) in free form or being derivatized so as to be immobilized to a water insoluble support; and contacting the free form or immobilized compound with an epoxide hydrolase under conditions in which the epoxide hydrolase is enzymatically active, the contacting effective to form a complex between the compound and the epoxide hydrolase, in which the activity of the epoxide hydrolase so complexed is modified with respect to enzymatically active, uncomplexed epoxide hydrolase.

X = N, O, S or C;
Y' = N, O or S

at least one of R1-R4 = H; provided that R2 = H when X = N but R2 is not present when X = S or O; and R4 = H when Y' = N but R4 is not present when Y' = S or O;

R1, R3 = H, 1-20C alkyl, cycloalkyl, aryl, acyl or heterocyclyl.

INDEPENDENT CLAIMS are included for:

(1) a purification method for an epoxide hydrolase comprising immobilizing (II) to a water-insoluble support; and eluting an aqueous solution having an epoxide hydrolase in it through the support; and

(2) an affinity separations article comprising a water insoluble support defining an exposed surface and having an immobilized compound on it, the immobilized compound being derived from (I), and the compound being derivatized for immobilization through one of R1 or R3, the immobilized compound being capable of forming a complex with an epoxide hydrolase.

Z = O or S;
W' = C or S;

R1', R3' = 1-20C alkyl, cycloalkyl, aryl, acyl, heterocyclyl.

ACTIVITY - Antiinflammatory; respiratory; cytostatic; immunosuppressive; antibacterial; gastrointestinal; tranquilizer; vulnerary; hemostatic; antipyretic; hypotensive. Male Swiss Webster mice were pretreated i.p. with dicyclohexylurea suspended in corn oil (400 mg/kg) or corn oil as positive controls. After 30 minutes of the pretreatment, the mice were treated intravenously through the tail vein with a 1:1 mixture of **leukotoxin**/isoleutotoxin methyl esters in ethanol. The mice died of respiratory distress after exposure to **leukotoxin/isoleukotoxin**. However, pretreatment with N,N'-dicyclohexyl-urea either blocked the animal death or lengthened the lives of the mice. IC50 of (I) is less than 500 micro M (claimed).

MECHANISM OF ACTION - Epoxide-hydrolase inhibitor.

USE - (I) are epoxide hydrolase inhibitors useful for the treatment of inflammation e.g. adult respiratory distress syndrome or in conjunction with a cancer therapy. (I) may also be used for treating sepsis, pancreatitis, multiple trauma such as brain injury, hemorrhagic shock, immune-mediated organ injury, fever and hypertension. The method is useful for inhibiting an insect epoxide hydrolase, fungal epoxide hydrolase or to reduce mycotoxic production by fungi; for purifying or isolating a microsomal epoxide hydrolase (the compound is derivatized so as to be immobilized to a water insoluble support); for inhibiting a mammalian soluble or microsomal epoxide hydrolase; and for inhibiting a plant epoxide hydrolase.

ADVANTAGE - (I) are biologically stable.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B10-A11A; B10-A11B; B10-A12A; B10-A12B; B10-A12C; B10-A13B; B14-A01; B14-C03; B14-C04; B14-E10; B14-F02B; B14-G02; B14-H01; B14-J01B4; B14-K01; C10-A11A; C10-A11B; C10-A12A; C10-A12B; C10-A12C; C10-A13B; C14-A01; C14-C03; C14-C04; C14-E10; C14-F02B; C14-G02; C14-H01; C14-J01B4; C14-K01

TECH UPTX: 20001006

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: The first step includes converting a precursor form of the compound before forming the complex. The precursor form of the compound is a carbodiimine or thiourea. The compound is capable of establishing anionic bond with a carboxylic acid residue of a protein, to stabilize one or more hydrogen bonds or to have a group able to establish a hydrogen bond with a tyrosine residue over the catalytic site. The modified activity of the epoxide hydrolase when in the complex is epoxide hydrolase inhibition. The epoxide hydrolase of the complex is selectively formed with a soluble epoxide hydrolase. The compound reduces the conversion of lipid epoxides to the corresponding diols. The compound is provided in combination with a plant growth regulator, a herbicide, an insect growth regulator, an insecticide or a fungicide.

L110 ANSWER 2 OF 2 WPIX (C) 2002 THOMSON DERWENT

AN 1998-159182 [14] WPIX

CR 2000-543662 [47]

DNC C1998-051324

TI Treating inflammatory disease with inhibitor of epoxy hydrolase - to prevent formation of pro-inflammatory **diol** metabolites of fatty acids, also new di ol(s) and antibodies against them, particularly for adult respiratory distress syndrome.

DC B04 B05 D16

IN BORHAN, B; CHEEK, J M; FERGUSSON, J; GRANT, D F; GREENE, J F; **HAMMOCK, B D**; MATOBA, K; MOGHADDAM, M F; SISEMORE, M F; ZHENG, J; GOODROW, M H; MORISSEAU, C H; SANBORN, J; SEVERSON, T

PA (REGC) UNIV CALIFORNIA

CYC 79

PI WO 9806261 A1 19980219 (199814)* EN 53p A01N033-02

RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

AU 9740692 A 19980306 (199830)

EP 926951 A1 19990707 (199931) EN

R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

US 5955496 A 19990921 (199945) A61K031-34

US 6150415 A 20001121 (200101) A61K031-17

US 6174695 B1 20010116 (200106) C12Q001-34

ADT WO 9806261 A1 WO 1997-US14385 19970813; AU 9740692 A AU 1997-40692 19970813; EP 926951 A1 EP 1997-938335 19970813, WO 1997-US14385 19970813; US 5955496 A Provisional US 1996-23397P 19960813, US 1997-909523 19970812; US 6150415 A Provisional US 1996-23397P 19960813, CIP of US 1997-909523 19970812, US 1999-252148 19990218; US 6174695 B1 Provisional US 1996-23397P 19960813, Div ex US 1997-909523 19970812, US 1999-312207 19990514

FDT AU 9740692 A Based on WO 9806261; EP 926951 A1 Based on WO 9806261; US 6150415 A CIP of US 5955496; US 6174695 B1 Div ex US 5955496

PRAI US 1997-909523 19970812; US 1996-23397P 19960813; US 1999-252148 19990218; US 1999-312207 19990514

IC ICM A01N033-02; A61K031-17; A61K031-34; C12Q001-34
ICS A01N037-02; A01N043-20; A01N043-24; A61K031-13; A61K031-23; A61K031-335; C07D307-12

AB WO 9806261 A UPAB: 20010126
Inflammatory disease is treated by administration of an inhibitor of epoxy hydrolase (EH). Also claimed are: (1) a method for detecting EH inhibition by treating cell cultures having a known level of free intracellular calcium ion with a tetrahydrofuran **diol** (II; metabolite of arachidonic acid (AA)) or a **leucotoxindiol** (III; metabolite of a **leucotoxin** epoxide) and determining the change in Ca ion level; (2) poly- or mono-clonal antibodies (Ab) against (II), and (3) an isolated biologically active (II).

(I) inhibit formation of (II) or dihydroxy lipids and is an antisense molecule; substrate mimic; chalcone oxide (particularly 4-(phenyl or fluoro)chalcone oxide); a phenyl glycidol (especially S,S-4-nitrophenylglycidol); a lipid alkoxide (especially 9-methoxystearic acid) or a lipophilic carbodiimide (especially dicyclohexyl carbodiimide). In the assay of (1), insect cells transfected with a baculovirus expressing EH may be used. Alternatively, to identify agents with reduced side effects in vivo, mammalian cells, especially pulmonary alveolar epithelial cells, are used and calcium influx is monitored.

USE - The method is specified for treatment of adult respiratory distress syndrome (ARDS), but can also be used to treat other diseases mediated by polyunsaturated lipid metabolites, e.g. systemic inflammatory response syndrome. The method (1) is used to identify (I) and Ab are useful for detection and purification of (II), for determining susceptibility to ARDS and for monitoring the progress or treatment of this condition (or of diabetes or other inflammatory diseases). Also (not claimed) **leucotoxins**, (III), (II) and other oxylipins are useful as (pro)drugs, e.g. as antimicrobials in animals and plants. (III) may also be a selectable marker for recombinant plants or used for control of plant pathogens. The process is based on the discovery that (II) and (III), and not their epoxide precursors as previously thought, are responsible for symptoms of ARDS and increase inflammation. Dosage of (I) is 0.001-100 mu mole/kg/day, given orally, parenterally or as a suppository.

Dwg.0/2

FS CPI

FA AB; DCN

MC CPI: B10-A24; B14-C03; B14-D07C; D05-H08; D05-H09; D05-H11

=> d his

(FILE 'REGISTRY' ENTERED AT 16:28:38 ON 21 JUN 2002)
DEL HIS
E LINOLEIC ACID/CN
L1 1 S E3
L2 5 S C18H32O2/MF AND 9 12 OCTADECADIENOIC ACID NOT (LABELED OR (D

FILE 'HCAPLUS' ENTERED AT 16:30:25 ON 21 JUN 2002
E LEUKOTOXINDIOL

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L3          15 S E1,E4,E5 (L) DIOL

     FILE 'REGISTRY' ENTERED AT 16:32:01 ON 21 JUN 2002
L4           1 S 189191-41-1
L5          10 S C18H34O4/MF AND 12 OCTADECENOIC ACID  AND 9 10 DIHYDROXY NOT
L6          10 S L4,L5

     FILE 'HCAPLUS' ENTERED AT 16:33:44 ON 21 JUN 2002
L7          33 S L6
L8          39 S L3,L7
L9         100 S (L1 OR LINOLEIC ACID)(L)DIOL
L10        125 S L8,L9
L11          8 S L10 AND (?HYPERTENS? OR ARDS OR (ADULT OR ACUTE)(L)RESPIR?(L)
               E HAMMOCK B/AU
L12        510 S E3-E8
               E ZUREK G/AU
L13          8 S E3,E4
               E GEE S/AU
L14        148 S E3-E10,E21,E22
               E NEWMAN J/AU
L15         81 S E3,E29
               E NEWMAN JOHN/AU
L16        318 S E3,E36,E37
L17         12 S L10 AND L12-L16
               E CARDIOVASCULAR/CT
               E E6+ALL
L18         67 S E1
               E E2+ALL
L19       5360 S E4
L20     281115 S E3+NT
               E HYPERTENSION/CT
               E E3+ALL
L21      33653 S E2+NT
               E E8+ALL
L22      23168 S E3+NT
L23      40210 S E8+NT
L24     118127 S E7+NT
               E ADULT RESPIRATORY DISTRESS SYNDROME/CT
               E E3+ALL
L25         31 S E1
L26       1395 S E2
               E PREECLAMPSIA/CT
               E E3+ALL
L27       2169 S E3,E4,E2+NT
L28       3737 S E3-E9/BI
               E LIPID METABOLISM/CT
               E E3_ALL
               E LIPID METABOLISM/CT
               E E3+ALL
L29      11021 S E1,E2
L30          6 S L10 AND L18-L29
L31         14 S L11,L17,L30
               E FATTY ACIDS/CT
               E FATTY ACIDS(L)D/CT
               E UNSATURATED FATTY ACIDS/CT
               E E3+ALL
L32       8133 S E1,E2
L33         48 S L32 (L) (DIHYDROXY# OR DIOH OR DIOL OR DI HYDROXY# OR DI OH)
L34         13 S L33 NOT (PLASTIC# OR COATING?)/SC,SX
L35          3 S L34 AND (1 OR 9 OR 63)/SC,SX
L36        320 S L32 AND L18-L29
L37          5 S L36 AND 9/SC
               SEL DN 2
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L38           1 S L37 AND E1
L39         422 S L32 (L) (ANT OR ANST)/RL
L40           6 S L39 AND L36
                SEL DN 3
L41           1 S L40 AND E2
L42          15 S L31,L38,L41
L43           1 S L10 (L) (ANT OR ANST)/RL
L44           0 S L10 AND (BLOOD ANALYSIS OR URINALYSIS)
L45           8 S L10 AND ?ASSAY?
                SEL DN 1 2 5
L46           3 S L45 AND E3-E5
L47          16 S L42,L46
L48           0 S L10 AND ELISA
L49           7 S L10 AND (BLOOD OR URINE)
                E BLOOD/CT
                E E3+ALL
L50           4 S L10 AND E2+NT
L51           0 S L10 AND (E136+NT OR E139+NT OR E145+NT)
                E URINE/CT
                E E3+ALL
L52           0 S L10 AND E3+NT
L53           1 S L10 AND E2+NT
L54           5 S L10 AND E1+NT
                E URINE ANALYSIS/CT
                E E3+ALL
L55           0 S L10 AND E3,E2+NT
L56          24 S L47,L49,L50,L53,L54
L57           9 S L56 AND L1,L2
L58          16 S L56 AND ?LINOLE?
L59          17 S L57,L58
L60           7 S L56 NOT L59
L61           6 S L60 NOT WASP
L62          23 S L59,L61
                SEL DN 6 18 19 20 21 22 23
L63          16 S L62 NOT E1-E7
L64          16 S L63 AND L3,L7-L63
L65          14 S L64 AND LEUKOTOX?
L66          16 S L64,L65
L67           7 S LINOLE? (L) ?GLUCURON? (L) ?CONJUGAT?
                SEL DN 1
L68           1 S L67 AND E8
L69          16 S L66,L68
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 17:05:40 ON 21 JUN 2002
L70           3 S E9-E11

     FILE 'REGISTRY' ENTERED AT 17:05:59 ON 21 JUN 2002

     FILE 'HCAPLUS' ENTERED AT 17:06:08 ON 21 JUN 2002

     FILE 'REGISTRY' ENTERED AT 17:07:30 ON 21 JUN 2002
L71           1 S 73889-55-1

     FILE 'HCAPLUS' ENTERED AT 17:07:40 ON 21 JUN 2002
L72          13 S L71
L73           5 S L72 AND L12-L16
L74           1 S L72 AND L18-L29
L75           5 S L73,L74 AND L69
L76           8 S L72 NOT L75

     FILE 'REGISTRY' ENTERED AT 17:08:58 ON 21 JUN 2002
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     FILE 'HCAPLUS' ENTERED AT 17:09:11 ON 21 JUN 2002

     FILE 'BIOSIS' ENTERED AT 17:09:26 ON 21 JUN 2002
                  E HAMMOCK B/AU
L77           510 S E3,E4,E7-E9
                  E ZUREK G/AU
L78             6 S E3,E4
                  E GEE S/AU
L79           112 S E3,E8,E22,E23
                  E NEWMAN J/AU
L80           264 S E3,E29
                  E NEWMAN JOHN/AU
L81            19 S E3
L82            12 S E15
L83             3 S E16
L84             9 S L6,L71
L85           566 S ?LEUKOTOXIN?
L86            14 S L85 (L) DIOL
L87            18 S L84,L86
L88            16 S L77-L84 AND L87
L89             2 S L87 NOT L88
L90            18 S L87-L89
L91             3 S L90 AND 00520/CC
L92             3 S L90 AND CONFERENCE/DT
L93             3 S L91,L92
L94            15 S L90 NOT L93
                  SEL DN 8 13
L95             2 S E1-E2
L96             5 S L93,L95 AND L77-L95

     FILE 'BIOSIS' ENTERED AT 17:14:13 ON 21 JUN 2002

     FILE 'MEDLINE' ENTERED AT 17:14:30 ON 21 JUN 2002
L97            11 S L84,L86

     FILE 'WPIX' ENTERED AT 17:15:51 ON 21 JUN 2002
L98            30 S ?LEUKOTOXIN? OR ?LEUKO TOXIN?
L99             0 S L98 (L) DIOL
L100           10 S ?LEUCOTOXIN? OR ?LEUCO TOXIN?
L101            1 S L100 AND DIOL
L102           36 S LINOLEIC ACID (L) DIOL
L103            3 S LINOLEIC ACID (L) ?GLUCUR?
L104            0 S LINOLEIC (L) ?CONJUGAT? (L) ?GLUCU?
L105            5 S LINOLE? (L) ?GLUCU?
                  E HAMMOCK B/AU
L106           15 S E4
                  E ZUREK G/AU
                  E GEE S/AU
L107           12 S E3-E7
                  E NEWMAN J/AU
L108           54 S E3,E25
L109            2 S L98,L100,L102,L103,L105 AND L106-L108
L110            2 S L101,L109

     FILE 'WPIX' ENTERED AT 17:21:45 ON 21 JUN 2002
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